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Drinking Water Criteria Document for Molybdenum (Final Draft)

Life Systems, Inc., Cleveland, OH

Prepared for

Environmental Protection Agency, Washington, DC

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The Office of Drinking Water (ODW), U.S. Environmental Protection Agency has prepared a Drinking Water Criteria Document on molybdenum.
This Criteria Document is an extensive review of the following topics:

- Physical and chemical properties of molybdenum
- Toxicokinetics and human exposure to molybdenum
- Health Effects of molybdenum in humans and animals
- Mechanisms of toxicity of molybdenum
- Quantification of toxicological effects of molybdenum

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I. SUMMARY

Molybdenum is an element of the second transition series which is ubiquitous in nature. While it can exhibit oxidation states from 2- to 6+, only the 3+, 4+, 5+ and 6+ oxidation states are important in aqueous solution. Molybdenum is one of approximately fifteen trace elements that are essential to plants and animals.

While the average abundance of molybdenum in the earth's crust is 10^{-4}%, it can occur at concentrations of 0.5% in localized geological anomalies. The principal form is molybdenum disulfide (MoS_2), which is highly insoluble. Molybdenum is mined as a primary ore in several states in the West, principally Colorado and New Mexico, and is a byproduct of copper and uranium mining in Colorado, Utah, Arizona and other western states. It is smelted primarily near steel plants, where it finds its greatest use as a component of metal alloys. Molybdenum is also used in fertilizers, catalysts, lubricants and anti-corrosive agents.

Although the naturally occurring oxide and sulfide minerals of molybdenum are generally insoluble, the alkali metal molybdates, which are among the principal commercial forms, are highly soluble (40 to 67 g/100 mL water). The principal dissolved species in dilute aqueous solution is the molybdate anion, MoO_4^{2-}. This oxidation state (6+) is quite stable with respect to oxidation and reduction under typical aqueous conditions. Moreover, this form is relatively mobile in geologic materials, particularly in the alkaline soils and subsoils of the western United States.

Most surface and groundwaters contain low concentrations of dissolved molybdenum, generally on the order of 1 μg Mo/L. It is rare to find concentrations greater than about 5 to 10 μg Mo/L.

The rate of molybdenum absorption depends on a number of factors, including the chemical form of the molybdenum and animal species. Those chemical forms involving molybdenum in the hexavalent state, such as molybdenum trioxide, sodium molybdate and ammonium molybdate are readily absorbed, whereas molybdenite (MoS_2) is not. Several studies indicate that molybdate ingested in water is almost entirely absorbed (e.g., fasting rats absorbed 99% of an orally administered dose of sodium molybdate in six hours). Guinea pigs absorbed about 90% of an oral dose of MoO_3. Rats absorbed 60% of an orally administered dose of $^{99}MoO_3$ in 24 hours. Ponies, calves and sheep, on the other hand, absorbed only 25% to 50% of doses of sodium and ammonium molybdate. Human balance studies indicate that 30% to 70% of molybdenum in the diet is absorbed. No data exist concerning the human absorption of molybdenum ingested in drinking water or the bioavailability of molybdenum in the human diet.

Once absorbed, molybdenum rapidly appears in the blood and most organs. Following a single oral dose, in monogastric animals, maximum tissue concentrations are reached within one to three hours, after which tissue concentrations rapidly decline with biological half-lives of 1.5 to 20 hours.

The highest molybdenum concentrations are found in the liver, kidneys and bones of most laboratory animals. Other organs which absorb molybdenum (less than the liver and kidney, but more than other organs) are the adrenal in rats and humans, the pancreas in mice, the heart in pigs and the omentum in humans. Very little molybdenum crosses the placental barrier, and the livers of human newborns have been found to contain about 1/8 the molybdenum concentration found in adult livers.

For most species, including humans, the principal route of excretion is via the urine. For laboratory animals, 30% to 90% of the molybdenum is excreted in the urine. For humans, the urinary excretion of molybdenum is generally 60% to 80% of the total excretion. Biliary excretion does not play an important role.

There is no apparent bioaccumulation of molybdenum in animal or human tissues. A steady state situation is quickly reached whenever exposure is increased. When the exposure is withdrawn, tissue concentrations quickly return to normal levels. Newborn humans have lower concentrations of molybdenum in their tissues than adults. The tissue concentration in humans increases from birth until age 20 to 60 and then declines. However, people with severe renal dysfunction have significant molybdenum accumulations in the liver (1.3 times higher than controls).

The principal routes of molybdenum exposure in humans are drinking water, food and air. Water concentrations of molybdenum vary greatly, from not detected to 1,024 µg/L. Molybdenum is an essential trace element and the intake from the diet ranges from 44 to 1,000 μg/day, with an estimated average of 100 μg/day. Intake of molybdenum from air is estimated at 0.011 μg/kg/day. The contribution of drinking water to total molybdenum intake ranges from 0% to 95%. It is estimated that drinking water would be the predominant source of molybdenum if the water concentration exceeds 49 μg/L.

There is considerable variability in the acute toxicity of molybdenum, depending on the chemical form and the animal species. Generally, soluble molybdenum compounds such as molybdenum trioxide and ammonium molybdate are more toxic than insoluble compounds such as molybdenite. Single doses of 400 to 800 mg Mo/kg of soluble molybdenum compounds are lethal when administered intraperitoneally to guinea pigs. The lethal dose for repeated oral administration is 100 to 300 mg/kg/day for soluble molybdenum compounds administered to rats, guinea pigs and rabbits. Histological examination shows damage to livers, kidneys and sometimes to adrenals and spleens. Ruminants are more sensitive to molybdenum (on a mg/kg body weight basis) than monogastric animals with lethal doses on the order of 1/10 to 1/100 of those for monogastric animals.

Molybdenum acts as a biological antagonist to copper. As a result, the response of an animal to increased molybdenum can depend on the animal's dietary copper history. The addition of copper to the diet often, but not always, completely reverses the symptoms of molybdenum toxicity. Animals that are deficient in copper tend to be more susceptible to molybdenum toxicity than animals with normal copper stores. Sulfur compounds also play an important role in the copper-molybdenum interaction. Generally, sulfate alleviates molybdenum toxicity in monogastric animals and exacerbates it in ruminants.

Addition of molybdenum to the diets of animals at sub-lethal doses can give rise to a number of adverse effects. The most common response at lower doses (2 to 8 mg Mo/kg/day in rats) is a decreased growth rate. At higher doses (10 to 50 mg Mo/kg/day in rats) symptoms such as achromotrichia, alopecia, male infertility, testicular degeneration, diarrhea, anorexia and weight loss have been reported. An effect which is shared by a number of species (rats, rabbits, cattle and sheep) involves bone or joint abnormalities, often in the forelegs. This effect is observed in rats at 10 to 50 mg Mo/kg/day.

Guinea pigs are somewhat less sensitive than rats to molybdenum toxicity. They show decreased weight gains at doses of about 40 mg Mo/kg/day, and weight losses at doses above 160 mg Mo/kg/day. They can tolerate a single dose of 80 mg Mo/kg/day as ammonium molybdate administered intraperitoneally with no apparent effects. Guinea pigs are also susceptible to achromotrichia.

Rabbits display many of the symptoms of molybdenum toxicity observed in rats. At doses of about 30 mg Mo/kg/day rabbits develop symptoms such as anorexia, weight loss, alopecia, dermatosis, anemia and a foreleg deformity. A dose of 66 mg/kg/day has been reported to affect the rabbits' appetite and cause thyroid dysfunction. An increase in serum sulfhydryl groups was observed in rabbits administered 0.5 mg Mo/kg/day and higher.

No effect on the growth of pigs receiving 2 mg Mo/kg/day as sodium molybdate was observed over a four month period. However, these animals did have a lower liver copper concentration than the controls; an effect shared with other species on elevated molybdenum intake.

Cattle have been observed to develop severe diarrhea at molybdenum intakes (generally as sodium molybdate) of 4 to 7 mg Mo/kg/day. Other symptoms reported in cattle include emaciation, achromotrichia, lethargy, cessation of milk synthesis, foreleg abnormalities, infertility and testicular degeneration.

There is only one study that indicates (but does not prove) that sodium molybdate and potassium molybdate are mutagens. The only report of carcinogenicity involved a molybdenum pigment which contained both lead and chromium, both of which are believed to be carcinogens. Thus, any conclusions on the potential carcinogenicity of molybdenum are limited.

Reproductive/teratogenic effects were evaluated in mice exposed to 10 mg/L molybdenum in drinking water (about 1.5 mg Mo/kg/day) over several generations. This exposure led to increased early deaths of offspring, increased numbers of dead litters, maternal deaths and runts.

In addition to causing infertility in male rats and cattle, increased molybdenum in the diet of these animals has been observed to cause seminiferous tubule degeneration. The addition of molybdenum to the diets of ewes on a low copper intake led to an increase in congenital swayback in their offspring.

Molybdenum is known to play an important role as a co-factor in the metallo-enzymes (e.g., xanthine oxidase, aldehyde oxidase and sulfite oxidase). While it is difficult to produce a diet so low in molybdenum that a deficiency is created, it is generally accepted that molybdenum is a required micronutrient. Balance studies in humans have indicated retention at daily intakes of about 50 to 100 μg Mo/day (about 0.001 to 0.002 mg Mo/kg/day). The National Academy of Sciences (NAS) recommends an adequate and safe intake of molybdenum for infants of 0.03 to 0.06 mg/day. The recommended adequate and safe intake for adults (and children over eleven years of age) is 0.15 to 0.5 mg/day.

Researchers have recently shown that sodium molybdate may offer protection against mercuric chloride toxicity and esophageal cancer induced by a known carcinogen.

There is a paucity of data on the health effects of molybdenum in humans. One patient maintained on total parenteral nutrition without molybdenum supplementation developed symptoms of apparent molybdenum deficiency. Metabolic disorders, possibly genetic, causing a defect in the incorporation of molybdenum into enzymes have been reported in a few patients. Epidemiological studies in the U.S.S.R. revealed a high incidence of a gout-like disease in a molybdenum-rich province where the population was reported to have a daily intake of about 10 mg Mo (0.14 mg/kg/day for a 70-kg adult human). Increased levels of uric acid and molybdenum in blood were also reported. The mechanism proposed for the gout-like disease observed in the U.S.S.R. is an increased synthesis of xanthine oxidase. This enzyme is involved in purine metabolism, catalyzing the formation of uric acid from xanthine and hypoxanthine.

A study in India observed increased copper excretion in men with moderately elevated molybdenum intakes (0.003 to 0.03 mg Mo/kg/day).

A study of workers in a molybdenum smelter in Denver revealed very high levels of molybdenum in blood (up to 300 μg/L) and urine (up to 11 mg/L) of some of the workers. However, serum ceruloplasmin and uric acid levels were within the normal ranges, and no adverse effects that could be attributed to molybdenum were observed.

Several persons whose drinking water contained molybdenum concentrations up to 200 μg/L were studied. While increased intake of molybdenum was associated with increased urinary excretion, no adverse effects were observed and blood molybdenum concentrations were within the normal range.

There is some evidence that the retardation of growth observed in several animal species administered an excess of molybdenum may be due to a voluntary rejection of food. This is believed to be due to taste or an association with a gastrointestinal disturbance. However, there is also evidence that at least some of the growth depression results from an interference with nutrient utilization, perhaps because of a disturbance in protein synthesis.

The mechanism involved in the copper-molybdenum-sulfur interaction has been the subject of considerable research and debate. In ruminants, very low molybdenum concentrations result in tissue copper depletion. There is evidence that thiomolybdates can be formed systemically in monogastric animals and in the rumen of ruminants. These thiomolybdates may then combine with copper to form a biologically unavailable copper-molybdenum-sulfur complex. Ruminants are more sensitive to molybdenum toxicity, according to this theory, because of a greater capacity to form sulfides (which are needed to form thiomolybdates) in the rumen. This leads to tissue accretion of copper as it becomes tied up with the thiomolybdates.

The recommended one-day Health Advisory (HA) for children was calculated to be 2.7 mg/L. For adults this was calculated to be 9.5 mg/L. The ten-day HA for children was calculated to be 0.3 mg/L and for adults to be 1.0 mg/L. These HA levels were based on a No-Observed-Adverse-Effect level (NOAEL) of 27 mg/kg/day in guinea pigs administered a single intraperitoneal (ip) dose and assuming 100% absorption following oral ingestion. While the use of oral dose studies is preferred for HA calculations, none are available. The Adjusted Acceptable Daily Intake (AADI) value of 0.1 mg/L was calculated from a NOAEL of 0.006 mg/kg/day observed in studies of humans with elevated molybdenum in their drinking water. No calculations of excess cancer risk have been made.

The World Health Organization (WHO) has not established or recommended a limit for molybdenum in drinking water. The U.S.S.R. has a limit of 0.5 mg Mo/L in open water. The ACGIH has established a threshold limit value of 5 mg Mo/m^3 for soluble molybdenum compounds.

II. PHYSICAL AND CHEMICAL PROPERTIES

The chemistry of molybdenum, like other elements of the second transition series, is extensive because of its ability to exist in several oxidation states. Molybdenum exhibits oxidation states from 2- to 6+; however, the oxidation states below 2+ are generally found only in synthetic organometallic compounds. Of the remaining oxidation states, only 3+, 4+, 5+ and 6+ are important in aqueous solution. The oxides and sulfides of these oxidation states are the principal solid inorganic molybdenum compounds found in nature. While the natural crustal abundance of molybdenum is only about 10^{-4}%, several molybdenum minerals occur in localized geologic anomalies. Molybdenum disulfide (MoS_2) is found naturally in the mineral molybdenite and in conjunction with copper sulfide ores. It is the principal mineral exploited as an economic resource. Other important naturally occurring minerals which contain molybdenum are powellite ($CaMoO_4$,), wulfenite ($PbMoO_4$), ferrimolybdite ($Fe_2O_3 \cdot 3.52\ MoO_3 \cdot 10.4\ H_2O$) and ilsemannite ($Mo_3O_8$). Most of these minerals are only slightly soluble at the pHs and oxidation-reduction conditions normally encountered in drinking water sources (Rollinson 1973).

Molybdenum metal (Mo^0) is prepared from the sulfide ore by oxidation to molybdenum trioxide (MoO_3), which is reduced with hydrogen to the metal. The most important use of molybdenum metal is in the production of alloy steels The presence of small amounts of molybdenum in steels imparts added hardness, strength and resistance to corrosion. Molybdenum trioxide is the starting material for production of other important molybdenum-bearing industrial chemicals. While MoO_3 is only slightly soluble in water (0.49 g/L at 28°C), it dissolves readily in aqueous alkali to form molybdates. Sodium molybdate, Na_2MoO_4, and its dihydrate are produced commercially by the action of sodium hydroxide on MoO_3. Similarly MoO_3 dissolves in aqueous ammonia producing polymolybdates, $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$, $(NH_4)_4Mo_8O_{26}\cdot 5H_2O$, $(NH_4)_2Mo_2O_7$, or a mixture of polymolybdates. Ammonium heptamolybdate (81.5% MoO_3) and ammonium polymolybdate (85% MoO_3) are commercially available, the latter known as "Molybdic Acid, 85%." The high solubility of alkali metal molybdates makes these compounds very useful in the production of other industrial chemicals. Sodium molybdate is used in the manufacture of molybdate chrome orange pigments. It is also used as a corrosion inhibitor in glycol based antifreezes. In the metal finishing industry it is used to produce black protective and decorative coatings on metal surfaces. Molybdenum compounds derived from molybdate starting materials are widely used in industrial catalysts for hydrocracking, hydrodesulfurization, oxidation, polymerization and reforming (Climax Molybdenum Co. 1973).

While the naturally occurring oxide and sulfide minerals are generally insoluble in water, the alkali metal molybdates are very soluble. The principal dissolved species in dilute aqueous solution is the oxyanion of the 6+ oxidation state. This oxidation state is relatively stable with respect to oxidation and reduction under natural conditions. Figure II-1 shows the species oxidation potential, relative to the hydrogen electrode (Eh), plotted against the solution pH (Kaback 1977). The regions of redox stability for the predominant aqueous molybdenum species are depicted together with the

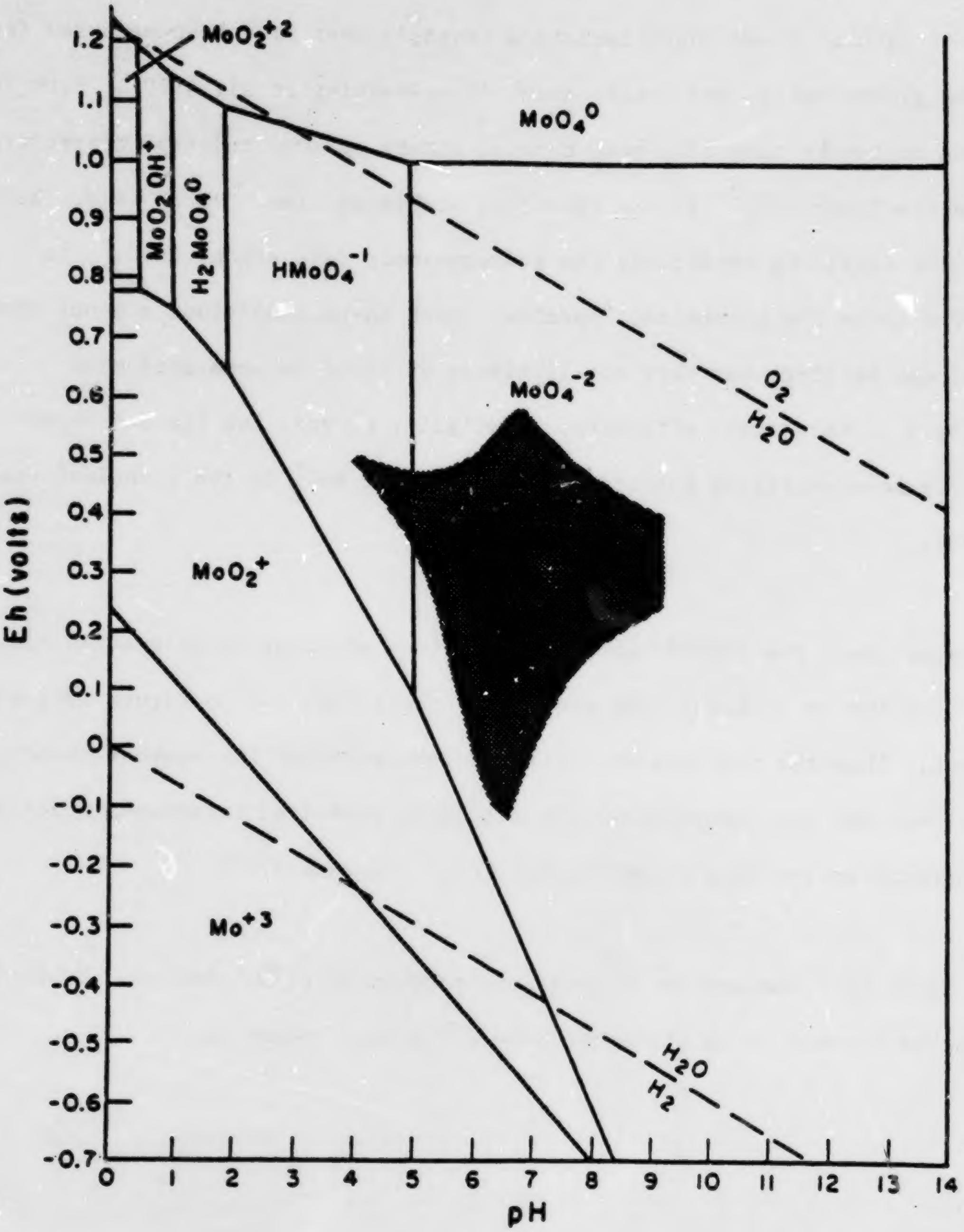

Figure II-1 Eh-pH Diagram of Areas of Predominance of Aqueous Species of Molybdenum (After Kaback 1977). Shaded Areas Shows Eh-pH Characteristics of Fresh Waters (After Baas-Becking et al. 1960).

range of natural Eh-pH characteristics (shaded) that have been measured for shallow ground waters and fresh waters (Baas-Becking et al. 1960). From this diagram it can be seen that most natural waters possess redox-pH characteristics which favor MoO_4^{2-} as the principal stable species. At pH values below 5 and under oxidizing conditions the hydrogen molybdate anion, $HMoO_4^-$, is expected to be the predominant species. Such Eh-pH conditions are not common in natural settings but they are likely to be found in some acid mine drainages or industrial effluents. Similarly, at very low pHs and under slightly less oxidizing conditions, the cationic MoO_2^+ is the principal species present.

When there are significant concentrations of other ionic species (such as iron, calcium or sulfate), the stability fields depicted in Figure II-1 may be changed. Thus the presence of other species can alter the aqueous chemistry of molybdenum, but nevertheless the principal dissolved molybdenum species in the natural environment is molybdate, MoO_4^{2-} (Kaback 1977).

Table II-1 summarizes the physical properties of molybdenum. Table II-2 lists the aqueous solubilities of some molybdenum compounds.

Table II-1 Physical Properties of Molybdenum

Color	Silver-white metal
Atomic number	42
Atomic weight	95.94
Specific gravity	10.2 g/cm^3 (20°C)
Melting point	2,617°C
Boiling point	4,612°C

Adapted from Weast 1974.

Table II-2 Aqueous Solubilities of Some Molybdenum Compounds

Chemical formula	Synonym	Solubility (g/100 mL)	Temperature °C
Mo	Molybdenum	insoluble	--
MoS_2	Molybdenum disulfide	insoluble	--
MoO_3	Molybdenum trioxide	0.49	28
$(NH_4)_2MoO_4$	Ammonium molybdate	38.65	20
$BaMoO_4$	Barium molybdate	0.0055	25
$CdMoO_4$	Cadmium molybdate	0.0067	25
$CaMoO_4$	Calcium molybdate	0.0050	25
Cs_2MoO_4	Cesium molybdate	67.07	18
$CuMoO_4$	Copper molybdate	0.038	20
$FeMoO_4$	Iron (II) molybdate	0.0076	20
$PbMoO_4$	Lead molybdate	0.000012	12
Li_2MoO_4	Lithium molybdate	44.81	25
K_2MoO_4	Potassium molybdate	64.57	25
Rb_2MoO_4	Rubidium molybdate	67.00	18
Na_2MoO_4	Sodium molybdate	39.38	25
$SrMoO_4$	Strontium molybdate	0.0216	25
$ZnMoO_4$	Zinc molybdate	0.37	25

Adapted from Weast (1974) and Climax Molybdenum Co. (1973).

III. TOXICOKINETICS

A. Absorption

Fairhall et al. (1945) studied the absorption of molybdenum trioxide in guinea pigs and rabbits of unspecified sex and strain. Three pairs of guinea pigs weighing 350 to 450 g were given 50 mg of molybdenum as MoO_3 in 10% gum arabic solution administered orally by syringe to the back of the animal's throat. The three pairs were retained in metabolism cages for 4 hours, 16 hours and 48 hours, respectively. At the end of each period, blood samples were taken and the animals were sacrificed. After four hours, 40% of the administered dose was found in the gastrointestinal tract, while only 4% had appeared in the urine and 0.2% in the feces. After 16 hours the percentages found in the gastrointestinal tract, urine and feces were 10%, 22% and 2%, respectively. After 48 hours, the percentages found in the gastrointestinal tract, urine and feces were 2.6%, 26% and 12%.

This rapid absorption following ingestion was confirmed by a further experiment whereby two rabbits weighing 1,880 g and 1,620 g were administered approximately 100 mg of MoO_3 by means of a stomach tube. Samples of blood were taken at 0, 10, 25, 40, 55, 70, 100, 160, 220, 280, 340 and 400 minutes after administration of the molybdenum. By 160 minutes the concentration of molybdenum in the blood of the first rabbit had increased from an initial value of 0.020 mg Mo/10 g blood to 0.056 mg Mo/10 g blood and from 0.013 mg Mo/10 g blood to 0.075 mg Mo/10 g in Rabbit No. 2 By 400 minutes (or 6 hours and 40 minutes after administration), the concentrations of molybdenum in the blood were 0.149 mg Mo/10 g in Rabbit No. 1 and 0.197 mg Mo/10 g in Rabbit No. 2 representing increases by factors of 7 and 14, respectively.

Arrington and Davis (1955) studied the absorption and excretion of ^{99}Mo administered orally to mature Long Evans rats of unspecified sex. The rats were randomly divided into two groups; one group was placed on a high Ca diet, the other served as control. After five weeks on these diets the rats were administered a dose of 15 µCi ^{99}Mo which was initially in the form of MoO_3 and had been neutralized and taken into solution with NaOH before dosing. The rats were confined to individual metabolism cages for separation and collection of urine and feces. At the end of the metabolism period the rats were sacrificed. Tissue samples were wet ashed in nitric acid and the radioactivity determined by a dipping tube fitted to a standard scaler. Results were calculated as the percentage of total dose excreted. These results are shown in Table III-1. There were no statistically significant differences between the two diet groups. The authors noted that the ^{99}Mo was absorbed and rapidly excreted mainly through the urine. They also noted that the "higher content of molybdenum in the kidney should be expected since the urinary system is the chief route of excretion."

Kosarek (1976) studied the kinetics of ^{99}Mo gastrointestinal absorption and tissue elimination in 41 out-bred male Sprague-Dawley rats weighing approximately 300 g. The rats were confined in metal metabolism cages for four days prior to dosing. They were fed Purina Lab Chow containing 1 to 3 mg/kg

Table III-1 Excretion of ^{99}Mo by Mature Rats Receiving Normal and High Calcium Diets

Ration	No. rats	Hours after dose	Urine (% of dose)	Feces (% of dose)
Control	10	6	26.38 ± 10.46[a]	
	6	12	50.82 ± 16.66	
	6	24	58.25 ± 15.98	7.98[b]
High Ca	9	6	24.43 ± 11.99	
	5	12	48.85 ± 16.17	
	4	24	55.73 ± 18.86	7.70[b]

[a] Standard deviation.

[b] Fecal excretions at 24 hours were highly variable in amount and in percentage of dose of excreted ^{99}Mo.

Adapted from Arrington and Davis (1955).

molybdenum (dry weight) and given distilled water to drink. They were allowed no food for 24 hours prior to dosing. The animals were anesthetized and ^{99}Mo was administered via an oral cannula to the stomach as sodium molybdate mixed with dehydrated bouillon. After dosing, the rats were returned to their metabolic cages and fecal and urine samples were collected. Groups of three to five animals were sacrificed at intervals of 1, 3, 6, 9, 12 15, 18, 21 and 24 hours and tissue samples were taken for analysis.

Absorption from the alimentary tract was found to occur with a half-life of 0.87 hour. After six hours, all but 1.26% of the total dose had been absorbed. Most of the absorption (81.57%) occurred in the stomach. The bulk of the remaining absorption (12.91%) took place in the upper small intestine.

Two groups of Swiss Webster mice weighing 22 to 25 g were given intravenous injections of 5 μCi of carrier-free ^{99}Mo (Rosoff and Spencer 1973). The dose was prepared from a solution of carrier-free ^{99}Mo in ammonium hydroxide diluted with saline and neutralized with hydrochloric acid (Rosoff and Spencer 1964). Both groups of mice consisted of three males and three females. One group of mice was sacrificed at one hour and the other at 24 hours after the injection. Urine and feces were collected for assay. Organs and tissue samples were removed at autopsy, weighed and radioassayed with a well-type NaI crystal gamma scintillation counter. The concentration of ^{99}Mo was highest in the liver, kidney and pancreas. At 24 hours 36.5% of the total dose had appeared in the urine and 2.6% in the feces.

Four pregnant Duroc sows were administered, by stomach tube, doses of ^{99}Mo and ^{45}Ca with a Na_2MoO_4 carrier in water solution (Shirley et al. 1954). Sows 1 and 2 weighed 135 and 140 kg, respectively, and were in their first pregnancy. Sows 3 and 4 weighed 152 and 136 kg, respectively, and were in their second pregnancy. Sows 1 and 2 were given 900 µCi doses of ^{99}Mo and 300 µCi of ^{45}Ca. Sows 3 and 4 received 3,160 µCi of ^{99}Mo and 870 µCi of ^{45}Ca. Carrier levels of 1.55, 3.10, 1.72, and 2.02 g of Na_2MoO_4, were administered to sows 1 to 4, respectively.

The sows were returned to metabolism racks and urinary and fecal collections continued until sacrifice 30 hours after receiving the ^{99}Mo dose. The fetuses were removed by abdominal hysterotomy. Blood samples were taken from the umbilical veins and the sows' hearts. Samples of fluids and tissues were taken from the fetuses and sows for assays. Determinations of ^{99}Mo were made with dipping-type Geiger tubes. Only the blood serum, livers and hearts of the fetuses showed more than a trace of the molybdenum isotope and these were about one-tenth of the concentrations in the corresponding sow tissues.

By 30 hours an average of 55% (range 37% to 74%) of the dose had been excreted in the urine and 8% (range 0.2% to 19%) in the feces and only an average of 3% (range 1% to 6%) remained in the alimentary tract.

Cymbaluk et al. (1981) reported the results of a study of the absorption and excretion of copper and molybdenum in ponies. Three ponies, one to two years of age, of unspecified sex and strain, were surgically fitted with bile duct cannulae. In two ponies the cannula consisted of silastic or PVC tubing placed in the bile duct below the union of the hepatic ducts. A collection tube of silastic or PVC tubing was connected to the bile duct tube and secured to the abdominal wall, then exteriorized through a stab incision in the cranial ventrolateral abdomen. The third pony had a T-tube placed in the bile duct. Maintenance of the ponies included twice daily oral administration of bile collected from the fistulated ponies and provision of feed and water. The studies were conducted one to two months post-operatively. The diet consisted of pelleted ration and hay fed at the rate of approximately 2% of body weight per day. The concentration of molybdenum in the feed was 0.9 to 1.5 ppm. The copper content was 8.5 to 10.4 ppm. The copper metabolism was assessed during a control period when the animals were fed the basal ration. The control period was followed by two consecutive periods of molybdenum addition to the basal diet. Molybdenum was added to the pelleted ration twice daily as $(NH_4)_6Mo_7O_{24}\cdot4H_2O$ in a 1:1 molasses-water solution. The mean molybdenum concentrations of the total feed were 1.01 ppm, 27.4 ppm, and 107.3 ppm for the basal, low and high molybdenum diets respectively. Adjustment periods to dietary changes lasted 8 to 14 days, followed by a six-day balance period when ^{64}Cu was received via nasogastric tube. The ponies were housed in metabolic stalls and complete collections of feces and urine were obtained.

Molybdenum was analyzed by flameless atomic absorption. The molybdenum balance for the ponies is shown in Table III-2.

Miller et al. (1972) investigated ^{99}Mo metabolism in young cattle and swine. Five dairy-beef cross yearlings averaging 325 kg, eight 100 kg calves, and six 25 kg Duroc barrows were used. The sex of the animals was not

Table III-2 Molybdenum Balance in Ponies Fed Molybdenum

	Mo in diet in mg/100 kg/day		
	Basal	Low Mo	High Mo
Intake	2.37 ± 0.04[a,b]	65.41 ± 4.73[b]	260.88 ± 10.04[b]
Excretion			
(a) Feces	1.82 ± 0.06[b]	35.13 ± 10.69[c]	131.92 ± 17.75[c]
(b) Urine	1.08 ± 0.05[b]	25.32 ± 0.29[c]	111.19 ± 11.41[c]
(c) Bile	0.06 ± 0.01[b]	0.29 ± 0.12[c]	0.86 ± 0.17[c]
Absorbed	0.54 ± 0.01[b]	30.28 ± 8.23[c]	128.99 ± 5.20[c]
Retained	-0.59 ± 0.06[b]	4.71 ± 2.52[c]	16.93 ± 8.51[c]
% Absorbed	22.80 ± 2.33[b]	46.30 ± 13.44[c]	49.40 ± 5.13[d]
% Retained	-32.41 ± 4.96[b]	7.20 ± 4.27[c]	6.50 ± 3.15[d]

[a] Values are means ± S.D.
[b,c,d] Comparable Mo values with unlike superscripts are significantly different ($P<0.05$).

Adapted from Cymbaluk et al. (1981).

specified. Two experiments were performed. In experiment 1, the five yearling calves were placed in metabolism stalls enabling separate collection of urine and feces. After a four-day adjustment period, they each received single doses of 2 mCi ^{99}Mo as $(NH_4)_2MoO_4$. Three calves were given the ^{99}Mo in gelatin capsules by balling gun ("rumen dose"). Two calves received the ^{99}Mo in warm water through nipple pails ("abomasal dose"). Blood, urine, feces and saliva were collected over a 72-hour period and assayed for ^{99}Mo activity.

The authors refer to the dose in nipple pails as the abomasal dose because water solutions suckled from nipple pails pass directly into the abomasum, bypassing the rumen. The two different dosing methods led to differences in blood ^{99}Mo levels and fecal and urinary excretion of ^{99}Mo by the calves. The highest blood levels of ^{99}Mo were found in the first blood sample taken eight hours after the abomasal dose and exceeded by over four times the highest ^{99}Mo level measured after the rumen dose. The blood levels from the abomasal-dosed calves dropped in subsequent samples and a biological half-life of 19 hours was determined. However, in the rumen-dosed calves blood levels of ^{99}Mo did not peak until 24 hours after dosage.

Total urinary excretion over 72 hours following the abomasal (nipple pail) dose was 26.7% of the dose compared to 10% for the capsule-dosed calves. Fecal excretion over that period was 37% for the nipple-pail dosed animals compared to 61.6% for the capsule-dosed calves.

The eight younger calves and six pigs were used in Experiment 2. The calves received doses of ^{99}Mo and ^{144}Ce^{144}Pr twice daily for seven days. (The authors do not mention whether the calves were placed in metabolism stalls.)

Four calves received the radioisotope in milk suckled from nipple pails ("abomasal dose") and four calves were dosed by capsule ("rumen dose"). The pigs were placed in metabolism stalls and administered daily doses of ^{99}Mo and ^{144}Ce^{144}Pr in their ration which was given to them three times a day for seven days. (The ^{144}Ce^{144}Pr was included as a non-absorbed reference material.) Blood, urine and feces were collected from the calves but not the swine. All animals in Experiment 2 were sacrificed on the eighth day. Digestive tracts were removed and divided into the gastric stomach, three sections of equal length of small intestine, cecum and colon. The reticulo-rumen omasum and abomasum of the calves were also separated. Contents of each section were mixed, weighed and assayed.

As with the single dose (Experiment 1), fecal excretion of ^{99}Mo predominated following daily rumen dosing. However, urinary excretion for the abomasal-dosed animals was consistently more (by approximately a factor of 2 for days five to seven) than fecal excretion. Blood ^{99}Mo levels during abomasal dosing stayed approximately constant from day one to seven, whereas blood ^{99}Mo concentrations from rumen doses increased throughout the seven-day period reaching a maximum value of about half that from the abomasal dose.

Apparent absorption from various sections of the digestive tract was calculated using ^{144}Ce^{144}Pr as a non-absorbed reference material. Total absorption of ^{99}Mo after seven daily doses averaged 74.8% for the six pigs, 29.8% from rumen doses for four calves and 62.2% for the four calves receiving the abomasal doses. The ^{99}Mo was absorbed from each section of the digestive tract from the gastric stomach through the small intestine. No appreciable ^{99}Mo absorption was apparent from the rumen or omasum, but net ^{99}Mo absorption by calves was doubled when these compartments were bypassed.

Kelleher et al. (1983) investigated the absorption of three labeled molybdenum compounds (tetrathiomolybdate, trithiomolybdate and sodium molybdate) in sheep fitted with re-entrant cannulae in the ascending duodenum. The animals were drawn from a pool of five male Texel sheep, weighing from 41 to 47 kg. They were arranged in pairs in adjacent metabolism cages and digesta from the animal given ^{99}Mo compounds was pumped anaerobically from the cannula into the second animal. Duodenal digesta from the second animal passed to the first to replace the "pumped" digesta. The authors state that maintenance of fluid equilibrium was the main problem encountered and for this reason the animals were kept on the experiment for only 120 hours. The animals were fed twice daily. The labeled compounds were given by stomach tube into the rumen of an animal already exchanging digesta with its partner. Only one pair of animals was used for each compound. Blood, urine and fecal samples were collected and assayed for ^{99}Mo.

While appreciable amounts of ^{99}Mo appeared within five minutes after dosage in the plasma of the animals receiving ^{99}Mo as thiomolybdates, only traces appeared in the plasma of the pair of animals given ^{99}Mo as molybdate until more than 60 minutes had passed. For all three compounds, overall absorption was higher from the post-cannula stage. The urinary output of ^{99}Mo for the molybdate-dosed animals was 25% in the second animal compared to 0.6% for the infused animal. Fecal excretion for the infused animal was <0.5% compared to 48.4% over 120 hours for the second animal.

Tipton et al. (1969) reported on a long-term balance study of dietary intake and excreta in humans. In this study, the food, feces and urine of two males were analyzed for molybdenum and several other trace elements. Molybdenum analyses were performed by arc emission spectroscopy. The studies were done over 50 weeks. One subject (Subject C) was 23 years of age, 187 cm tall and weighed about 100 kg. The other (Subject D) was 25 years old, 178 cm in height and weighed about 71 kg. Each subject collected estimated duplicates of every item that he ate and drank. They also collected urine and feces. The average dietary intake of molybdenum for subjects C and D was 0.21 and 0.46 mg Mo/day, respectively. The mean urinary output was 0.11 and 0.13 mg Mo/day for subjects C and D, respectively. The authors state that "subject D may have overestimated and subject C underestimated his dietary intake since subject D appears to have been in positive balance and C in negative balance for several elements including essential elements like magnesium and potassium." Using urinary output as a measure of absorption, these two subjects absorbed 52% and 28% of molybdenum in their diet.

Robinson et al. (1973) conducted a metabolic balance study of molybdenum and other elements in four 19- to 21-year-old New Zealand women. Each experiment lasted 27 days. The diet consisted of meat loaf, ice cream, tea and coffee (and orange juice for two of the subjects). Each subject chose her own level of fluid intake, but kept it constant. Distilled water was used for all beverages. Brilliant blue was used as an intermittant fecal marker and for two of the subjects chromic oxide was used as a continuous fecal marker.

Samples of the diet, feces and urine were collected and analyzed (molybdenum was determined spectrophotometrically with dithiol). The mean percentage of dietary intake recovered from urine ranged from 29% to 57% while the percentage recovered in the feces ranged from 38% to 72%.

Engel et al. (1967) described a balance study in 36 pre-adolescent girls (six to ten years old) in the southeastern U.S. (Blacksburg, VA). The study took place over three periods of time (1956, 1958 and 1962). Each period involved 12 girls and the diets differed from one period to the next. The children were housed on the campus where the study was performed for the entire study period. Collections were made of urine and feces. The food, urine and feces were analyzed spectrophotometrically using thiocyanate. The mean percentage of dietary intake found in the urine ranged from 38% to 70%, whereas the mean percentage of dietary intake found in the feces ranged from 17% to 33%.

The results of these molybdenum absorption studies are summarized in Table III-3.

B. Distribution

Fairhall et al. (1945) in the reference cited in Section III.A. also studied the distribution of molybdenum in tissues of white rats and guinea pigs exposed to various forms of molybdenum by various routes.

Table III-3 Summary of Molybdenum Absorption Studies

Reference	Species	Form	Route	Dose (mg Mo/kg)	% Absorption[a]	% Urine
Fairhall et al. (1945)	Guinea Pig	MoO_3	Oral	111-142	60 (4 hrs) 88 (16 hrs)	
Arrington and Davis (1955)	Rat	$^{99}Mo\text{-}Na_2MoO_4$	Oral	Tracer		56-58 (24 hrs)
Kosarek (1976)	Rat	$^{99}Mo\text{-}Na_2MoO_4$	Stom. Tube	Tracer	99 (6 hrs)	
Rosoff and Spencer (1973)	Mouse	^{99}Mo	IV	Tracer		36 (24 hrs)
Shirley et al. (1954)	Pig	$^{99}Mo\text{-}Na_2MoO_4$	Stom. Tube	12	89 (30 hrs)	55 (30 hrs)
Cymbaluk et al. (1981)	Pony	$(NH_4)_6Mo_7O_{24}$	Food	2	23	
				65	46	
				261	49	
Miller et al. (1972)	Cow	$^{99}Mo\text{-}(NH_4)_2MoO_4$	Water/Milk	Tracer	62	27 (72 hrs)
			Capsule	Tracer	30	10 (72 hrs)
	Pig	$^{99}Mo\text{-}(NH_4)_2MoO_4$	Diet	Tracer	75	
Tipton et al. (1969)	Human (M)	Unknown	Diet	Endogeneous		28-52
Robinson et al. (1973)	Human (F)	Unknown	Diet	Endogeneous		29-57
Engel et al. (1967)	Human (F)	Unknown	Diet	Endogeneous		38-70

[a] $\%\ \text{Absorption} = \frac{\text{Total} - (\text{GI} + \text{Feces})}{\text{Total}}$

In one experiment reported by these authors, white rats (sex and strain not reported) were divided into five groups. One group was used as a control; the other four groups were given molybdenum as molybdenite (MoS_2), molybdenum trioxide (MoO_3), calcium molybdate ($CaMoO_4$) and ammonium molybdate ($(NH_4)_2MoO_4$), respectively, incorporated in their food. At the end of the experimental period the surviving animals were sacrificed and their tissues were removed for chemical analysis and microscopic examination. All molybdenum analyses were performed using the thiocyanate method. The analyses indicated that the animals ingesting molybdenum trioxide stored somewhat more molybdenum in their tissues than those ingesting calcium molybdate (Table III-4). Storage was least in the molybdenite group "probably due to the low order of solubility of molybdenite in the digestive juices."

In another experiment, molybdenum trioxide or calcium molybdate (25 mg Mo/mL, suspended in 10% gum arabic solution) were administered in various dosages to guinea pigs each day. The material was delivered to the back of the animal's throat by means of an hypodermic syringe provided with a blunt-ended needle.

The animals were sacrificed at the end of the test and their tissues analyzed for molybdenum (by the thiocyanate method). The distribution (Table III-5) of molybdenum in tissues showed a greater deposition than was obtained in the ingestion experiments described earlier with particularly high values in the liver and kidney.

Table III-4 Distribution of Mo in Tissues of White Rats After Ingestion of Mo Compounds

Compound	No. of animals used	Estimated daily consumption (mg Mo)	No. of days on test	Estimated total intake of Mo (grams)	Average final weight (grams)		Average final weight (grams)		Average dose mg/kg/day based on initial weights		Average Distribution in tissues (mg Mo/10 g fresh tissue)		
					Died	Killed	Died	Killed	Died	Killed	Liver	Kidney	Bone
Molybdenite	8	10	44	0.4	--	82	--	151	--	122	0.02	0.04	0.06
	8	100	44	4.4	--	79	--	146	--	1,266	0.02	0.06	0.05
	8	500	44	22.0	--	79	--	153	--	6,329	0.01	0.04	0.06
Molybdenum Trioxide	8	10	120	0.9	82	83	91	103	122	120	0.12	0.11	0.23
	10	25	137	1.8	128	183	73	106	195	137	0.08	0.19	0.25
	10	50	137	1.7	140	197	95	140	357	254	0.36	0.33	0.40
	8	100	14	1.1	77	--	58	--	1,299	--	0.24	0.14	--
	8	500	8	3.1	81	--	66	--	6,173	--	0.49	0.39	--
Calcium Molybdate	10	9	137	0.9	143	112	121	140	62.9	80.4	0.04	0.12	0.25
	10	21	128	1.3	122	--	109	--	172	--	0.05	0.21	0.28
	10	43	137	3.2	149	134	102	142	298	320	0.09	0.17	0.34
	10	86	57	3.6	189	--	110	--	455	--	0.08	0.17	0.79
	10	430	17	4.7	175	--	113	--	2,457	--	0.18	0.35	0.37
Ammonium Molybdate	8	10	232	2.3	73	82	102	144	137	122	0.09	0.36	--
	8	100	13	1.0	78	--	58	--	1,282	--	0.16	0.16	0.41
	8	500	9	3.2	85	--	--	60	5,882	--	0.16	0.08	--
Control (Average)	48	0	137	0.0	112	121	140	175	0	0	0.03	0.06	0.05

Adapted from Fairhall et al. (1945).

Table III-5 Distribution of Mo in Tissues of Guinea Pigs After Oral Administration of Mo Compounds

Compound	No. of animals used	Estimated daily consumption (mg Mo)	No. of days on test	Estimated total intake of Mo (grams)	Average final weight (grams)		Average final weight (grams)		Average dose mg/kg/day based on initial weights		Average Distribution in tissues (mg Mo/10 g fresh tissue)		
					Died	Killed	Died	Killed	Died	Killed	Liver	Kidney	Bone
Calcium Molybdate	8	25	95	2.1	468	452	485	750	53.4	51.5	0.07	0.31	0.19
	8	100	95	7.3	459	473	280	697	218	211	0.16	0.47	0.36
	8	200	95	14.8	488	430	416	684	410	465	0.16	0.62	0.81
Molybdenum Trioxide	8	25	99	1.4	293	286	331	550	85	87	0.38	0.52	0.82
	8	100	27	1.1	330	--	304	--	303	--	1.06	1.03	0.78
	8	200	9	3.5	343	--	333	--	483	--	1.81	2.59	2.01

Adapted from Fairhall et al. (1945).

In the experiment by Arrington and Davis (1955) described earlier in which Long-Evans rats were given an oral dose of ^{99}Mo as molybdenum trioxide, the tissues of the animals were assayed for uptake of ^{99}Mo. The results are shown in Table III-6. Molybdenum was found in all tissues examined, with the highest levels occurring in the kidney.

In the work by Kosarek (1976) described earlier in Section III.A., rats were given ^{99}Mo orally as sodium molybdate. Table III-7 gives the time to maximum concentrations in various tissues as well as the maximum concentrations reached in various tissues.

In the work by Rosoff and Spencer (1973) described in Section III.A., Swiss Webster mice were given an intravenous injection of ^{99}Mo. One group of mice was sacrificed at 1 hour and the other at 24 hours, and the ^{99}Mo content of various tissues was measured. The results are shown in Table III-8. Molybdenum was found throughout the body, with the highest levels occurring in the liver and kidney.

In the experiment by Shirley et al. (1954), where four pregnant sows were given doses of ^{99}Mo by stomach tube, tissue samples from both the sows and the fetuses were assayed. Table III-9 shows the distribution of the ^{99}Mo in the tissues of the sows that were sacrificed at 30 hours.

Flanjak and Lee (1979) determined the trace element content of liver and kidney samples from cattle obtained in Australia. These organs were taken from a total of 190 cattle in eight locations in New South Wales. The

Table III-6 Tissue Distribution of ^{99}Mo in Mature Rats Receiving Normal and High Calcium Diets

Ration	No. rats	Hours after dose	Percentage of dose per gram tissue				
			Blood	Liver	Kidney	Muscle	Femur
Control	6	6	0.345 ± 0.094[a]	0.185 ± 0.085	0.457 ± 0.210	0.129 ± 0.028	0.277 ± 0.114
	6	24	0.038 ± 0.023	0.021 ± 0.009	0.054 ± 0.016	0.008 ± 0.0045	0.036 ± 0.010
High Ca	5	6	0.327 ± 0.078	0.144 ± 0.023	0.349 ± 0.108	0.091 ± 0.066	0.243 ± 0.175
	6	24	0.035 ± 0.017	0.021 ± 0.004	0.091 ± 0.046	0.019 ± 0.014	0.058 ± 0.037

[a] Standard deviation

Adapted from Arrington and Davis (1955).

Table III-7 Time After Administration of Oral Dose of ^{99}Mo To Reach Maximum in Tissues and Maximum Concentrations

	Time to reach maximum (hrs)	Maximum Concentration in % dose/g (except blood)
Whole Blood	3	0.192%/mL
Liver	1	0.14
Spleen	6	0.08
Adrenals	1	0.19
Kidneys	3	0.33
Gonads	3	0.079
Urine	1-3	0.91
Gastrocnemius Muscle	1-3	0.026
Femur	3-6	0.097

Adapted from Kosarek (1976).

Table III-8 Tissue Concentrations of ^{99}Mo in Mice

Tissue	^{99}Mo, % Dose/g[a] 1 hour	24 hours
Liver	18.1	18.0
Kidney	11.6	9.0
Pancreas	4.7	3.0
Lung	2.3	1.1
Bone	2.0	0.6
Spleen	1.9	1.4
Ovaries[b]	1.9	1.3
Skin	1.8	1.0
Heart	1.4	0.8
Testes[b]	1.1	1.3
Muscle	0.8	0.3
Whole Blood	1.6	0.2

[a] Values are averages from six mice.
[b] Values are averages for three mice.

Adapted from Rosoff and Spencer (1973).

Table III-9 Distribution of ^{99}Mo in Tissues of Sows as Percent of Dose per Gram

Tissue	First Pregnancy	Second Pregnancy
Blood Serum	0.2[a]	--
Whole Blood	--	0.23
Kidney	0.80 ± 0.60[b]	0.28 ± 0.20
Liver	0.70 ± 0.02	1.00 ± 0.10
Pancreas	0.07 ± 0.04	0.04 ± 0.01
Spleen	0.21	0.39 ± 0.05
Brain	0.05 ± 0.01	0.04 ± 0.02
Heart	0.65 ± 0.03	1.04 ± 0.03
Gastrocnemius Muscle	none	trace
Small intestine	--	trace
Large intestine	--	0.60 ± 0.30
Femur	0.70 ± 0.30	0.40 ± 0.17
Vertebra	0.65 ± 0.40	--

[a] Standard deviation not sufficient to give values to first two decimal places.
[b] Mean and standard deviation.

Adapted from Shirley et al. (1954).

samples were packed in polyethylene bags. No information is given about the strain, sex, weight or diet of the cattle. The analyses were performed by atomic spectroscopy. The detection limit was reported as 0.15 μg Mo/g (fresh weight). They observed a mean of 0.88 μg Mo/g tissue fresh weight in the livers, with a range from below the detection limit to 2.41 ug Mo/g. In the kidneys they observed a mean content of 0.31 μg Mo/g fresh weight with a range from below detection limit to 1.85 μg Mo/g. Three percent of the livers and 16% of the kidneys had molybdenum concentrations below the detection limit.

Froslie and Norheim (1976) reported the results of a study of molybdenum in livers of sheep and lambs collected from 16 different districts of Eastern Norway. A total of 128 sheep and 192 lambs of unspecified strain and sex were involved. The animals were described simply as "grazing" animals and neither weights nor ages were specified. The mean concentrations (μg Mo/g wet weight) and standard deviations for the adult sheep and lambs were 1.0 ± 0.3 and 0.9 ± 0.3, respectively. The authors state that this difference is significant (P<0.001).

Meinel et al. (1979) determined the contents of molybdenum and other trace elements in the livers of 9 human newborns and 37 adult humans. The cause of death of the newborns was maternal complication during late pregnancy (age range from 23 weeks gestation to birth) or delivery. None of the nine cases exhibited signs of malformation or inborn metabolic errors. The adult livers were obtained on autopsy. Samples were taken only when the histological diagnosis of the liver showed no significant pathological change. Those patients who had diseases known to influence the trace element contents in the liver were excluded. Five of the infants were males and twenty-three of the adults were males. The mean age of the adults was 69 years. The analyses were performed by proton-induced X-ray emission (PIXE).

The mean molybdenum content of the newborns' livers was 0.1 μg Mo/g (wet weight) compared to 0.76 μg Mo/g (wet weight) for the adults. This difference was found to be highly significant ($P<10^{-7}$). The authors speculate that because of the antagonistic relationship between molybdenum and copper, the low molybdenum levels in the newborns might be related to their results showing the newborn livers contained an average of 103 μg Cu/g compared to the average for the adult livers of 6.5 μg Cu/g. This result was determined to be highly significant ($P<10^{-7}$).

Tipton and Cook (1963) reported the results of an extensive study of trace element content in human tissue. They measured 27 elements in 29 tissues of 150 adult (age > 20 years) subjects in the U.S. They used spectrographic analysis and reported the values as μg/g of tissue ash. They also gave the mean, median and standard deviation for ash as % of wet and dry weight. No distribution of the subjects by sex was given. The detection limit for molybdenum was 4 μg/g of ash. They observed that most tissues had less than the detection limit except for the liver which had a mean molybdenum content of 81 μg/g ash. The mean ash weight of the liver was 1.3% of the wet weight and 3.7% of the dry weight. This result is consistent with the results of Meinel et al. (1979).

Tipton et al. (1968) reported a study of the variation with age of elemental concentrations in human tissue. The work involved the data obtained by Tipton and Cook (1963) previously discussed plus data on 23 children. They found a slight but significant decrease with age of molybdenum in the livers of humans (data from 157 individuals).

Allaway et al. (1968) analyzed samples of human blood obtained from blood banks for molybdenum concentration. Nineteen blood banks throughout the U.S. were asked to supply pilot tubes from male donors. The blood from one site was collected in connection with pre-employment checks. An attempt was made to avoid large cities as collection sites. The molybdenum contents were measured by the thiocyanate method. The detection limit was 0.5 μg Mo/100 mL. Molybdenum in concentrations greater than the detection limit were found in less than one-fifth of the samples. Mean values were calculated for each city which had samples with molybdenum above the detection limit. Only samples above the detection limit were included in the mean. Only nine cities had detectable amounts and the means ranged from 0.5 μg Mo/100 mL to 15.73 μg Mo/100 mL. However, only one city was above 3 μg Mo/100 mL. The highest value recorded for an individual was 41 μg Mo/100 mL. Both the highest individual value and the highest city average were obtained from Missoula, Montana.

Schroeder et al. (1970) measured the molybdenum content of tissues obtained from 27 routine autopsies in San Francisco. The data were obtained by emission spectroscopy. The limit of detection was 2 μg/g ash. The ash weight is about 1% of wet weight. Table III-10 gives the results of the analyses of several tissues (the sex of the subjects was not specified although it would appear that at least 18 were males). Several other tissues (muscle, uterus, bladder, esophagus, trachea, and skin) were analyzed but were found to be below the detection limit. Little or no molybdenum was detected in the gastrointestinal tract, except for the jejunum.

Chappell et al. (1979) reported a study of plasma molybdenum concentrations and other parameters in human subjects. These subjects consisted of 24 research personnel at the University of Colorado Medical Center (who served as controls) and 25 workers at a local smelter where molybdenite is converted to MoO_3. An industrial hygiene survey showed that the average daily exposure of the workers was approximately 1.65 mg Mo/m^3 in the form of MoO_3 (in respirable-size dust particles). The sex distribution of the subjects was not specified. Based on a survey of food in the Denver area performed by Tsongas et al. (1980), it was estimated that the total dietary intake of molybdenum for the subjects was between 0.12 and 0.24 mg Mo/day (0.002 to 0.003 mg Mo/kg/day, assuming a 70-kg person). Thus, the factory workers were potentially exposed to 70 to 139 times as much molybdenum as the controls (assuming 10 m^3 of air is inhaled in eight hours).

Blood samples were taken from the subjects and the plasma molybdenum concentrations were measured by flameless atomic absorption. The detection limit was 0.005 mg Mo/L. Fourteen of the control subjects had plasma molybdenum concentrations below the detection limit. In the ten remaining

Table III-10 Molybdenum in Human Tissues

Tissue	No. of cases	No. found	μg/g ash
Adrenal	27	27	14.0 ± 0.75[a]
Aorta	27	5	<2
Brain	24	17	2.0 ± 0.23
Diaphragm	26	25	3.0 ± 0.27
Stomach	27	21	3.0 ± 0.36
Jejunum	26	23	5.5 ± 0.52
Sigmoid Colon	26	10	2.5 ± 0.49
Rectum	23	8	2.0 ± 0.42
Omentum	22	19	12.0 ± 1.40
Lung	27	23	2.7 ± 1.6
Heart	27	27	3.8 ± 0.17
Liver	27	27	53.0 ± 3.70
Kidney	27	27	15.0 ± 0.74
Pancreas	27	25	3.2 ± 0.37
Spleen	27	21	4.2 ± 0.62
Testis	18	16	3.1 ± 0.38
Prostrate	20	14	3.9 ± 0.83
Thyroid	12	10	3.4 ± 0.63
Fat	27	27	5.1 ± 0.79

[a] Mean values ± SEM, detection limit 2 μg/g ash.

Adapted from Schroeder et al. 1970.

subjects the molybdenum concentrations ranged from 0.005 to 0.034 mg Mo/L. By contrast, among the factory workers, plasma molybdenum ranged from 0.009 to 0.365 mg Mo/L and all were above detection limit. Levels of 0.035 to 0.100 mg Mo/L were present in the plasma of seven of the 24 workers and eight had plasma molybdenum concentrations above 0.100 mg Mo/L. The differences between blood molybdenum in the controls and factory workers were highly significant ($P<0.005$) by the Wilcoxon Rank Sum Test.

C. Metabolism

The study of the metabolism of molybdenum has been greatly complicated by the differences between ruminants and non-ruminants (Suttle 1980) and the interaction between copper, molybdenum and sulfur. The purpose of this document is to focus on the form of molybdenum found in drinking water (namely, the molybdate anion, $MoO_4^{=}$) and on health effects in humans. Thus this discussion will ignore the data on ruminants because they are not good models for humans and will also ignore the effects of varying amounts of dietary copper and sulfur. The issue of high risk populations that have low dietary intakes of copper and sulfur is briefly addressed in Section VI.C. The interaction with copper and sulfur is addressed in Section VII.C.

In the work by Fairhall et al. (1945) which was described in Section III.A., three pairs of guinea pigs were given 50 mg of molybdenum as MoO_3 or 110 to 140 mg Mo/kg (since the authors stated that the animals weighed 350 to 450 g). Each pair was retained in metabolism cages for 4 hours, 16 hours and 48 hours, respectively. They were then sacrificed and tissue samples taken for molybdenum analysis by the thiocyanate method. Table III-11 shows the results of the analyses.

In the work by Kosarek (1976) described earlier, the ^{99}Mo content in various tissues was followed for a 24 hour period following oral administration of labeled sodium molybdate to white rats. After an initial rise to a maximum of 0.192% dose/mL after three hours, the blood ^{99}Mo concentrations decreased to approximately 0.002% dose/mL and was fit by the curve:

$$\% \text{ Dose/mL} = 0.60e^{-0.385t} + 0.021e^{-0.097t}$$

with corresponding biological half-lives of 1.80 and 7.15 hours, respectively.

Several tissues demonstrated an initial increase followed by a decrease (which could be characterized by one or two half-lives) to a residual level. These results are shown in Table III-12.

The urinary excretion was fit by the curve (for $t > 3$ hours):

$$\% \text{ of Dose} = 100 - 467.7e^{-0.864t} - 21.22e^{-0.0189t}$$

with corresponding half-lives of 0.82 hour and 36.67 hours.

Somewhat similar results, but for fewer tissues and time intervals were obtained by Arrington and Davis (1955) and were discussed in Section III.B. (See Table III-6).

Table III-11 The Absorption and Distribution of Mo Following Oral Administration of Molybdenum Trioxide to Guinea Pigs

Tissue	(mg Mo/10g tissue) 4 hours	16 hours	48 hours
Kidneys	0.46	0.20	0.07
Spleen	0.26	0.12	0.18
Blood	0.26	0.05	0.50
Bile	0.28	0.20	0.30
Liver	0.20	0.08	0.03
Lungs	0.31	0.10	0.09
Muscle	--	0.20	0.01
Feces (total Mo)	0.10	0.90	5.80
Urine (total Mo)	2.20	11.10	13.20
Gastrointestinal Trace (total Mo)	19.90	5.80	1.29

[a] The authors stated that the bone values were inconsistent and suggested this was due to the short period of exposure. Therefore, they did not include these values.

Adapted from Fairhall et al. (1945).

Table III-12 Summary of Half Lives and Residual Amounts of ^{99}Mo in Tissues of Rats

Tissue	Maximum concentration % dose/g	1st $t_{1/2}$ (hr)	2nd $t_{1/2}$ (hr)	Update $t_{1/2}$ (hr)	Residual % Dose/g
Whole Blood	0.19%/mL	1.80	7.15	--	none
Liver	0.14	1.46	--	--	0.071
Spleen[a]	0.08	--	19.3	--	0.028
Adrenals[b]	0.19	3.03	--	7.97	0.019
Kidney	0.33	1.65	--	--	0.039
Gonads	0.079	2.16	--	--	0.016
Gastrocnemius Muscle	0.026	2.16	--	--	0.009
Femur	0.097	1.76	--	--	0.010

[a] The author could not fit a curve to the first decrease from 6 to 9 hours. But from 9 to 24 hours the decrease followed an exponential with a 1/2 life of 19.3 hours.

[b] The adrenal concentrations first declined from 1 hour to 15 hours with a 1/2 life of 3.03 hours, but then showed an increase with a 1/2 life of 7.97 hours.

Adapted from Kosarek (1976).

In the work by Shirley et al. (1954) discussed earlier, the tissues of fetuses were assayed for ^{99}Mo content after the sows were sacrificed 30 hours after receiving the dose by stomach tube as a ^{99}Mo tracer in a sodium molybdate carrier. The results are shown in Table III-13.

Rosoff and Spencer (1964) studied the metabolism of ^{99}Mo in four human patients. The patients, their age, sex and diagnosis are listed in Table III-14.

The dose of ^{99}Mo was prepared from a solution of carrier-free ^{99}Mo in ammonium hydroxide, diluted with saline, and adjusted to pH 7 with hydrochloric acid. A single tracer dose of 500-100 μCi was injected intravenously. Blood, urine and fecal samples were collected for analysis. The blood levels were followed for 24 hours. Urine and fecal samples were collected for 5 to 13 days.

The authors reported that the levels of ^{99}Mo disappeared rapidly from the vascular compartment. At one hour the concentrations in whole blood and plasma ranged from 2.5% to 5% of dose. The levels in both whole blood and plasma decreased rapidly with less than 0.5% remaining at 24 hours. The concentration in whole blood was slightly higher than in the plasma at all times.

The urinary excretion differed from one patient to the next, but in all cases was highest on the first day and generally decreased on following days. A total of 16.6% to 27.2% of the dose was eliminated by urine in five days.

Table III-13 Distribution of Isotope in Tissues of Pig Fetuses as Percent Dose per Gram (10^{-4})[a]

Tissue	First pregnancy	Second pregnancy
Amnion	--	0.12
Amniotic Fluid	0.08 ± 0.03	0.05 ± 0.01
Allantois	--	0.09
Allantoic Fluid	--	0.24 ± 0.11
Placenta	0.11	0.14 ± 0.04
Uterus	0.36 ± 0.19	--
Blood Serum	Trace	0.03 ± 0.02
Liver	0.07 ± 0.05	0.02 ± 0.01
Heart	Trace	0.02

[a] The blood cells, kidney, brain, gastrocnemius muscle, femur and vertebra were also assayed but had traces or less of activity.

Adapted from Shirley et al. (1954).

Table III-14 Patients Receiving ^{99}Mo

Patient	Age	Sex	Diagnosis
1	65	F	Carcinoma of breast with metastases
2	53	F	Perivasculitis
3	78	F	Carcinoma of breast with metastases
4	69	M	Metastic epidermoid carcinoma

Adapted from Rosoff and Spencer (1964).

Fecal excretion was much less (1% to 6.8% cumulative in two patients followed for ten days).

These results are, of course, complicated by the fact that the patients were suffering from terminal illnesses and could well have been metabolizing molybdenum differently from healthy human adults. But they do show the rapid movement out of the blood and the importance of urinary elimination seen in most non-ruminants, especially rats.

D. Excretion

In addition to the studies by Fairhall et al. (1945) described in Section III.C., where excretion by guinea pigs given a dose of 110 to 140 mg Mo/kg was monitored for 48 hours after the oral dose in the form of MoO_3, the authors also described a more detailed experiment on molybdenum excretion. In this study, which used two guinea pigs of unspecified strain and sex, MoO_3 was administered orally for a total of ten days and the animals were weighed daily. The total amount of molybdenum administered was approximately 200 mg. Since one animal weighed about 0.7 kg and the other about 0.6 kg this dose was about 285 mg Mo/kg for animal 1 and 333 mg Mo/kg for animal 2. The 24-hour output of urine and feces was analyzed for each of five days preceding administration (fore period), during the ten days in which the animals received molybdenum (experimental period) and for eight days following the experimental period (after period).

During the fore period the average weight of animals 1 and 2 was 0.67 and 0.47 kg, respectively. Their average urinary molybdenum excretion was 0.2 mg/day and 0.3 mg/day, respectively and their average fecal excretion was 0.09 mg/day for each. By the second day of the experimental period the urinary and fecal excretion for animal 1 was 16.1 mg/day and 3.5 mg/day respectively, and 12.7 mg/day and 3.3 mg/day for animal 2. For the next eight days (days 3 to 10 of experimental period) the average urinary and fecal excretion of animal 1 was 16.1 mg/day and 6.2 mg/day, and 11.2 mg/day and 3.0 mg/day for animal 2. During the experimental period the animals were receiving approximately 20 mg/day of molybdenum or (since their average weights were 0.69 and 0.58 kg, respectively during this period), 29 mg Mo/kg/day and 34 mg Mo/kg/day, respectively.

By the second day of the after period (or day 17 of the total study period) their urinary and fecal excretion had dropped to 5.1 mg/day and 2.2 mg/day (animal 1) and 3.5 mg/day and 3.0 mg/day (animal 2). By the fourth day of the after period, urinary and fecal excretion were 0.5 mg/day and 0.3 mg/day (animal 1) and 0.6 mg/day and 0.1 mg/day (animal 2), respectively. Table III-15 summarizes the excretion data. The authors point out that it was difficult to administer the intended amount and suggest that this is the explanation for the total excretion of the first animal of 17% more and of the second animal of 19% less than the 200 mg of molybdenum administered. Again, these results indicate, as noted in other experiments, a rapid and near total absorption and a rapid and near total excretion mostly by means of the kidneys when a soluble form of molybdenum is administered orally.

Table III-15 Excretion of Mo Following Oral Administration to Guinea Pigs

Time Period	Excretion (mg Mo/day)			
	Urine		Feces	
	Animal 1	Animal 2	Animal 1	Animal 2
Fore period	0.2	0.3	0.09	0.09
Experimental period (Day 2)	16.1	12.7	3.5	3.3
Experimental period (average of Day 3 to 10)	16.1	11.2	6.2	3.0
After period (Day 2)	5.1	3.5	2.2	3.0
After period (Day 4)	0.5	0.6	0.3	0.1

Adapted from Fairhall et al. (1945).

A similar result was obtained by Arrington and Davis (1955) as discussed in Section III.A., where Table III-1 shows that by 24 hours after oral administration of a ^{99}Mo tracer to rats as MoO_3, 56% to 58% of the dose had been excreted in the urine and 8% in the feces.

In the work by Kosarek (1976) discussed earlier, where an oral dose ^{99}Mo was given to rats as sodium molybdate, he observed that 87% and 1% of the dose had appeared in the urine and feces, respectively, after 24 hours.

Kinnamon (1966) studied the effect of various diets on the excretion of molybdenum and zinc in pregnant rats. In his work on molybdenum he used 96 Sprague-Dawley rats, six weeks of age. They were assigned at random to 8 groups of 12 each. The control group received a basal diet (molybdenum content unspecified). The other groups had various amendments which included various combinations of copper, molybdenum and sulfate. One group received the basal diet with 0.02% molybdenum added as sodium molybdate. The groups were maintained on their respective rations for a period of four weeks before normal male Sprague-Dawley rats were placed with the females for five days. At the end of six weeks and two days each animal was administered a 50 μCi dose of ^{99}Mo as molybdate (unspecified salt) by stomach tube. The animals were sacrificed 48 hours later. Urine, feces and blood samples were collected as were fetal and placental tissue. The animals were weighed throughout the period, but no weights were reported for the group given ^{99}Mo (however, the average weight gain for the two groups on the basal and molybdenum diets which received ^{65}Zn tracer was 0.125 kg and 0.109 kg, respectively). Thus, at the time of ^{99}Mo dosing the animals weighed about 0.2 kg (assuming they started at 0.1 kg) and (assuming a consumption of 15 g of food/day with 1 ppm for the controls and 200 ppm for the high molybdenum group) the daily dose rate at the end of the experiment was 0.075 mg/kg/day for controls and 15 mg/kg/day for the high molybdenum group. After 48 hours 2.37%/100 g wet weight and 0.08%/100 g wet weight of the ^{99}Mo dose was observed in the fetuses of the control and high molybdenum group, respectively. Thus, the fractional transport of molybdenum to the fetuses tended to decrease in the high-molybdenum group, although the absolute amount of molybdenum being transferred was increased (approximately seven times higher in the high molybdenum group receiving 200 times the amount of molybdenum).

The percentage of the dose excreted in urine after 24 hours was 24.41 in the control group and 78.70 in the high molybdenum group, respectively. During the next 24 hours 8.29% and 1.68% of the ^{99}Mo dose was excreted in the urine of the control and high molybdenum dose groups, respectively. The total fecal excretion in the two groups was 8.17% of the ^{99}Mo dose in the controls and 2.94% in the high molybdenum group. The excretion of ^{99}Mo was affected by various additions of copper and/or sulfate as will be discussed later. But the addition of molybdenum alone to the diet had the effect of significantly ($P<0.01$) increasing the urinary excretion of ^{99}Mo.

Lener and Bibr (1979) studied biliary excretion and tissue distribution of ^{99}Mo as sodium molybdate in 40 male Wistar (substrain Konarovice) rats. The rats had a mean body weight of 230 g and were kept in groups of five.

Twenty animals received injections of 0.08 mg ^{99}Mo/kg and another twenty rats received 4.6 mg ^{99}Mo/kg in the tail vein one hour after cannulation of the bile duct through an abdominal incision while under anesthesia. Bile was collected at 3 minute intervals for the first two hours after injection and at 30 minute intervals for the next two hours. Tissue contents were determined at 1, 2, 3 and 4 hour intervals after the 4.6 mg/kg dose. Only 1% of the total amount of administered ^{99}Mo was excreted via bile. The concentration reached a peak in about one hour after injection and then rapidly declined reaching a value of about 1/2 maximum at four hours after injection.

As noted in Section III.A., Rosoff and Spencer (1973), injected Swiss Webster mice with ^{99}Mo and collected urine and feces for a 24 hour period before they were sacrificed. They found that 36.5% of the total dose had appeared in the urine versus 2.6% in the feces after 24 hours.

The experiment by Shirley et al. (1954) where four swine were given a ^{99}Mo tracer in a sodium molybdate carrier, administered orally, was also discussed in Section III.A. By 30 hours after administration of the ^{99}Mo an average of 54.77% of the dose had appeared in the urine and 8.19% in the feces. The range for urinary and fecal output during that period for the four sows was 36.9% to 74.1% and 0.23% to 18.9%. The average total excretion during the 30 hour period was 63% of the total ^{99}Mo dose with a range from 50.3% to 81.1%.

A study of molybdenum and copper balance in ponies (Cymbaluk et al. 1981) was described in Section III.A. From Table III-2 it can be seen that fecal excretion accounted for more than half of total excretion (a range of 61% for the basal diet to 54% for the high molybdenum diet) and biliary excretion accounted for less than 3% (only 0.4% in the high molybdenum case).

In a study of ^{99}Mo metabolism in cattle (Miller et al. 1972) described earlier (Section III.A.), it was observed that during the 72 hours following a single dose of ^{99}Mo administered in milk suckled from nipple pails (abomasal dose), 37.0% of ^{99}Mo was excreted in the feces and 26.7% was excreted in the urine. The rumen-dosed animals excreted 61.6% in the feces and 10% in the urine.

The excretion pattern for sheep is similar to that of cattle and horses. The work by Kelleher et al. (1983) described in Section III.A. indicates that more molybdenum is excreted in the feces than in the urine.

In the study reported by Tipton et al. (1969) described earlier in Section III.A., two human male adults were followed for 50 weeks. Their dietary intake and excretion of molybdenum was measured during this time. It was found that for one subject (subject C) 55% of the total excretion of molybdenum (urine plus feces) was by way of urine, whereas for the other subject 57% was by way of urine. However, it is important to note that the method used for chemical analysis (arc emission spectrography) is not a very sensitive or reliable method for molybdenum.

Robinson et al. (1973) studied the molybdenum balance in four young women. This study was also described earlier in Section III.A.

Table III-16 gives the dietary intake and the ratio of urinary and fecal excretion of molybdenum to daily intake. The study took place over two years 1966 and 1967. Subjects D and W were studied in 1966 and subjects G and M in 1967. There is a striking difference between dietary intakes during the two periods. The dietary intakes in the 1966 study are much lower than those reported by Schroeder et al. (1970), which were 0.090 to 0.460 mg/day or, Tsongas et al. (1980) which for 19 to 21 year-old women were approximately 0.15 mg/day. It is possible that problems were encountered with molybdenum analyses and/or sample collection in the 1966 period.

In the work by Engel et al. (1967) described previously in Section III.A., a balance study was conducted on 36 pre-adolescent girls. Table III-17 shows the dietary intake and excretion of molybdenum for the three different study periods. Again there are some sizeable differences in dietary intake, particularly between 1956 and 1958. Furthermore, Tsongas et al. (1980) found that girls in the age range of 6 to 11 years had an average intake of about 170 μg/day or between 0.005 and 0.007 mg Mo/kg. The differences here could reflect unusual dietary choices, problems with sampling and/or analytical error.

Schroeder et al. (1970) reported a balance study on five human subjects. The age, weight and sex of the subjects were not given. Table III-18 summarizes their results.

As mentioned in Section III.C., Rosoff and Spencer (1964) studied the excretion of a ^{99}Mo dose administered to four human subjects. Two of the

Table III-16 Daily Balance of Molybdenum in Three Female Subjects

Subject (year)	Average daily intake (mg)	Ratio of average urinary output to daily intake	Ratio of average fecal output to daily intake
D (1966)	0.048	0.31	0.72
W (1966)	0.046	0.29	0.68
G (1967)	0.091	0.57	0.46
M (1967)	0.096	0.57	0.45

Adapted from Robinson et al. (1973).

Table III-17 Average Micronutrient Molybdenum Balance (24-hour) in Pre-Adolescent Girls

Year	No. of subjects	Average weight of subjects kg	Intake μg	Fecal μg	Urine μg	% Urine of total Mo excretion
1956	3	24	72.4	23.8	40.4	63
	3	27	74.0	21.0	46.4	69
	3	31	74.9	21.3	50.2	70
	3	33	80.8	21.4	56.5	73
1958	12	28	47.7	8.1	28.3	78
	12	29	43.2	8.3	27.1	77
1962	6	27	46.5	11.7	22.7	66
	6	29	71.2	11.9	26.7	69

Adapted from Engle (1967).

Table III-18 Molybdenum in Diets and Excreta in Long-Term Balance Studies on Five Human Subjects[a]

Subject	Mean Intake		Route of Excretion	
	Days	mg/day	Feces (Mean %)	Urine (Mean %)
A[b]	30	0.099	21	79
B	30	0.101	37	63
C	347	0.210	48	52
D[c]	347	0.460	42	57
E	70	0.110	73	27

[a] All analyses were performed by emission spectroscopy.

[b] Subject A was in negative balance.

[c] Subject D was in positive balance.

Adapted from Schroeder et al. (1970).

subjects were followed for ten days. Their cumulative urinary excretion was 24% and 29% of the dose, respectively. Their cumulative fecal excretion was less than 1% and 6.8%, respectively. However, it was noted that the higher fecal excretion of ^{99}Mo for patient 2 resulted from the passage of 4% of the dose in one stool specimen on study day 4.

In the study of molybdenum smelter workers by Chappell et al. (1979) described in Section III.B., urine samples were collected from 14 of the 25 workers. An attempt was made to obtain complete daily samples, but these were judged to be incomplete as determined by daily urinary creatine excretions. Therefore, only urinary molybdenum concentrations are reported. For the control subjects the range of molybdenum concentration in urine was from 0.020 to 0.230 mg Mo/L. For the factory workers only two subjects were in the normal range, seven had urinary molybdenum concentrations in the range of 0.450 to 1 mg Mo/L, four were in the range of 1 mg Mo/L to 3 mg Mo/L and one subject had 11 mg Mo/L in his urine.

The same report (Chappell et al. 1979) described a study of miners who worked in a molybdenum mine where MoS_2 was extracted. Dust samples revealed a time weighted average of 0.32 to 1.32 mg Mo/m^3 respirable dust. Urine was collected from six of the workers and analysis showed a range of 0.026 to 0.085 mg Mo/L in their urine. This result is consistent with the animal studies by Fairhall et al. (1945) discussed in Section III.B. and reflects the very low solubility (and bioavailability) of MoS_2.

In addition to the worker studies, the same report also described the results of studies of urinary molybdenum excretion in several human subjects who were exposed to varying concentrations in their drinking water supply. These subjects lived in various Colorado communities where molybdenum in the water supply was monitored by the authors. Some of the subjects collected 24 hour urine specimens which were analyzed for molybdenum (all of these analyses were by graphite furnace atomic absorption). The weight, and in most cases, age and sex of the subjects was not specified. The results of this study are shown in Table III-19. These data show a tendency for urinary molybdenum excretion to increase with increased concentrations in drinking water. Unfortunately, individual dietary intakes and fecal excretion of molybdenum and copper were not obtained.

Table III-20 summarizes excretion data from the studies discussed.

E. Bioaccumulation and Retention

The studies by Fairhall et al. (1945), Arrington and Davis (1955), Kosarek (1976) and Rosoff and Spencer (1973) discussed in Section III.B. all show that the primary organs in guinea pigs, rats and mice where molybdenum concentrates are the kidney, liver and bone. Other organs of laboratory animals which were found to be high in molybdenum uptake were adrenals (Kosarek 1976--rats), pancreas (Rosoff and Spencer 1973--mice) and heart (Shirley et al. 1954--pigs).

Bibr et al. (1977) studied the fate of a single dose of ammonium molybdate labeled with ^{99}Mo. Male Wister rats (2 months old, unspecified weight) were maintained on Larsen chow containing less than 0.3 ppm Mo. Tap water was used (but molybdenum content was not specified). A single dose

Table III-19 Comparison in Urinary Mo Excretion of Subjects With Different Mo Concentrations in Drinking Water

Location	Number of Subjects	Concentration in Drinking Water (mg/L)	Estimated[a] Daily Intake mg/kg/day	Urinary Mo (mg/24 hours)	P-Value[b] Urinary Mo
Golden (1975)[c]	4	0.2	0.008	0.186 ± 0.03	<0.005
Golden (1977)	8	0.04	0.004	0.088 ± 0.01	
Denver[d]	9	0.04	0.004	0.088 ± 0.02	N.S.[e]
Denver Suburb[d]	9	0.1	0.005	0.097 ± 0.01	
Summit County[f]	4	0.01	0.003	0.072 ± 0.014	N.S.[e]
Summit County[f]	6	0.14	0.007	0.112 ± 0.032	
Summit County[g]	5	0.01	0.003	0.057 ± 0.009	<0.025
Summit County[g]	8	0.14	0.007	0.10 ± 0.014	

[a] Assumes food intake averaging 0.18 mg/day, water intake of 2 L/day and 70 kg body weight.
[b] P value for comparison between indicated pairs.
[c] 20-year old male college students.
[d] Workers at water treatment plant, sex unspecified.
[e] N.S. = Not significant at P = 0.05.
[f] Adult males with minimum two-year residence.
[g] Adult females with minimum two-year residence.

Adapted from Chappell et al. 1979.

Table III-20 Summary of Molybdenum Excretion Studies

Reference	Species	Form	Route	Dose (mg Mo/kg)	Excretion (% Dose) Urine	Feces	Bile
Fairhall et al. (1945)	Guinea Pig	MoO_3	Oral	285-333	73	27	
Arrington and Davis (1955)	Rat	$^{99}Mo\text{-}MoO_3$	Oral	Tracer	56-58	8	
Kosarek (1976)	Rat	$^{99}Mo\text{-}Na_2MoO_4$	Oral	Tracer	87	1	
Kinnamon (1966)	Rat	$^{99}Mo\text{-}MoO_4$	Stom. Tube	0.075	33	8	
				15	80	3	
Lener and Bibr (1979)	Rat	$^{99}Mo\text{-}Na_2MoO_4$	IV	4.6			1
Rosoff and Spencer (1973)	Mouse	^{99}Mo	IV	Tracer	36	3	
Shirley et al (1954)	Pig	$^{99}Mo\text{-}Na_2MoO_4$	Stom. Tube	12	55	8	
Cymbaluk et al. (1981)	Pony	$(NH_4)_6Mo_7O_{24}$	Diet	2	46	77	2.5
				65	39	54	0.4
				261	43	51	0.3
Miller et al. (1972)	Cow	$^{99}Mo(NH_4)_2MoO_4$	Water/Milk	Tracer	27	37	
			Capsule	Tracer	10	62	
Tipton et al. (1969)	Human	Unknown	Diet	Endogenous	28-52	22-42	
Robinson et al. (1973)	Human	Unknown	Diet	Endogenous	29-57	45-72	
Engel et al. (1967)	Human	Unknown	Diet	Endogenous	38-70	17-33	
Schroeder et al. (1970)	Human	Unknown	Diet	Endogenous	27-79[a]	21-73[a]	
Rosoff and Spencer (1964)	Human	Mo	IV	Tracer	24-29	1-7	
Chappell et al. (1979)	Human	Unknown	Water, Food	0.003-0.008	22-36		

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[a] Values expressed are % total excretion. Data not available to convert excretion to % dose.

of 50 to 100 µCi was injected subcutaneously and the rats were killed after 2, 4, 6, 10, 13.5 and 14 days. There were eight rats in each group. Organs were removed and assayed. The data for each organ were fitted by an equation which contained an excretion term and a retention term. The best fit was given for a retention constant of zero for kidney, liver, testes and cross-striated muscle. Only the skin had a non-zero retention constant. The excretion half-lives for the various organs were all about two to five hours.

As was discussed in Section III-B., Tipton and Cook (1963) analyzed human tissue. The molybdenum concentrations in most tissues, except liver, were below the detection limit. Furthermore, Tipton et al. (1968) observed a slight but significant decrease with age of molybdenum concentrations in the livers of humans.

Schroeder et al. (1970) analyzed several human tissues and observed the highest concentrations of Mo in the ash to be in the liver, kidney, adrenal and omentum (see Table III-10). The remaining tissues had molybdenum concentrations of roughly 1/3 to 1/10 of the previously mentioned tissues. The authors of that paper also reported a study of changes in molybdenum tissue concentration with age. There was somewhat less in subjects under 20 years of age (the authors do not report whether the difference was statistically significant). Liver molybdenum concentrations (in ash) were found to increase from birth until about age 20 years and then decrease until, at age 60 years, they were about that of age one year. Kidney concentrations were found to increase from birth until about age 30 years and then decrease slightly. Other organs showed some increase but only through the sixth decade.

As indicated in Section III.D., urinary excretion is an effective route for elimination of molybdenum. Thus it might be suspected that people with renal disturbances might not eliminate molybdenum as effectively as those with normal renal function. Smythe et al. (1982) analyzed autopsy tissues of 120 uremic patients on dialysis and 64 controls who died of other causes. Of the nine tissues analyzed (aorta, bone, brain, heart, kidney, liver, lung, muscle and spleen) molybdenum concentrations were measurable only in liver and kidney tissue. Table III-21 presents the molybdenum concentrations by weight of dry tissue. No statistically significant differences in molybdenum concentrations were found in kidney or liver tissues between the dialyzed and the non-dialyzed patients. Liver molybdenum concentrations were higher in both the dialyzed and the non-dialyzed patients as compared with controls.

The work by Engel et al. (1967) described in Section III.A. showed positive balances for molybdenum in the pre-adolescent, female subjects. All daily intakes reported were less than 0.085 mg/day (subject body weights not reported).

Tipton and Stewart (1970) reported a balance study of three adult male subjects. Results for two of the subjects, C and D, were discussed in Section III.A. (Tipton et al. 1969). Subject E was 174 cm in height and weighed 85 kg. Their ages were 23 (C), 25 (D) and 56 (E). The molybdenum analyses were performed by dc arc emission spectrography. The protocol was the same as in Tipton et al. (1969). The period of study was 50 weeks for subjects C and D and 20 weeks for subject E. The average dietary intake per day ranged from

Table III-21 Concentration of Mo in Autopsy Tissues of Humans with Chronic Uremia

Tissue	Control Subjects	Non-Dialyzed Patients	Dialyzed Patients
Kidney	1.16 ± 0.38 (44/44)[a]	0.44 ± 0.26 (12/18)[b]	0.38 ± 0.31 (17/48)[b]
Liver	3.52 ± 1.72 (46/46)	4.75 ± 2.05 (23/23)[c]	4.57 ± 1.66 (75/75)[b]

[a] Data expressed as the mean ± 1 SD (number measurable/number of samples).
[b] Significant when compared to control, $P<0.01$.
[c] Significant when compared to control, $P<0.05$.

Adapted from Smythe et al. (1982).

0.11 mg to 0.46 mg (0.001 to 0.006 mg/kg/day). The average differences between daily molybdenum intake and daily molybdenum excretion were found to be 0.01 mg (C), 0.23 mg (D), and 0.01 mg (E) with standard deviations of 0.03, 0.09 and 0.01, respectively. Thus, with the exception of subject D (who reported fecal samples for less than 1/2 of the total days of the study period), the subjects were close to balance.

In the balance study by Robinson et al. (1973), discussed in Section III.A., the authors reported that their subjects (four young women) were in balance with respect to molybdenum. The differences between dietary intake and excretion for dietary intakes ranging from 0.046 to 0.096 mg/day (approximately 0.001 mg/kg, assuming 70 kg) were 1% to 9%. Since the authors did not report analytical errors or variances due to day-to-day fluctuations, it is reasonable to assume that the differences between intake and excretion were less than experimental error.

F. Summary

The rate of molybdenum absorption depends on a number of factors, including chemical form and animal species. The chemical forms which involve molybdenum in the hexavalent state (molybdenum trioxide, sodium molybdate, and calcium molybdate) are readily absorbed whereas molybdenite is not. Guinea pigs were observed to absorb about 90% of an oral dose of MoO_3. Rats were observed to absorb 60% of an orally administered dose of $^{99}MoO_3$ in 24 hours and 99% (while in a fasting state) of an orally administered dose of labeled sodium molybdate in six hours. The half-life for gastrointestinal absorption in the latter experiment was 0.9 hours, with most of the absorption occurring (82%) in the stomach.

Pigs were observed to absorb 55% of an orally administered dose of sodium molybdate in a 30 hour period. Ponies were observed to absorb about 50% of a dose of ammonium molybdate mixed with their food. Calves were observed to absorb 30% of a dose of labeled ammonium molybdate administered in capsules (rumen dose) and 62% of a dose administered via nipple pails (abomasal dose). This difference may occur because of the interaction of molybdenum with copper and sulfur in the rumen. Sheep were observed to absorb 25% of a labeled dose of sodium molybdate over a 120 hour period.

Human balance studies have given results of 30% to 70% average absorption of molybdenum in the diet. Unfortunately, no data exist regarding the chemical form of molybdenum in human diets or its bioavailability. It appears reasonable to assume that some fraction (perhaps 50%) of molybdenum in the diet may not be readily absorbed. This would explain the somewhat lower absorption by humans than guinea pigs or rats.

Once absorbed, molybdenum rapidly appears in the blood and most organs. In most laboratory animals the highest concentrations of an absorbed dose are found in the livers, kidneys and bones. Experiments with molybdenite (MoS_2) showed essentially no uptake by tissues, even for doses as high as 6,000 mg/kg in rats. Rats receiving molybdenum as molybdenum trioxide, sodium molybdate or ammonium molybdate show approximately the same tissue distribution. For single doses, maximum concentrations in guinea pig tissues are reached in one to three hours and then the tissue concentrations begin to decline with biological half-lives of 1.5 to 20 hours.

Although the highest molybdenum concentrations in animal and human tissues are found in the liver, kidney and bone, molybdenum is found in lesser amounts in the other tissues. Other organs with a smaller concentration relative to liver and kidney, but of higher molybdenum concentration relative to other organs are the adrenals in rats and humans, the pancreas in mice, the heart in pigs and the omentum in humans.

Very little molybdenum seems to cross the placental barrier. The livers of human newborns have been found to contain about 1/8 the molybdenum concentration of those of adults.

Blood molybdenum concentrations for humans are normally about 0.005 mg Mo/L and may range up to 0.03 mg Mo/L. However, molybdenum smelter workers exposed to high levels of MoO_3 were found to have blood molybdenum levels as high as 0.360 mg Mo/L.

In most species, including humans, the majority of molybdenum is excreted via urine. For guinea pigs approximately 30% to 75% of the total molybdenum is excreted via urine. For rats the ratio of urinary to fecal excretion has been found to range from 3 to nearly 90 depending on the dose, the chemical form and the route of administration. The high value of 90 was found in fasting rats and might indicate that in fed animals molybdenum can be bound by food particles, making it unavailable. The relative amount of molybdenum excretion via urinary vs. fecal routes can also be affected by the amount of copper and sulfur in the diet.

Very little, perhaps 1% or less of the molybdenum excretion is via the bile.

The excretion pattern in mice is similar to that in rats, with more than ten times as much molybdenum appearing in urine as in feces when the animals were injected with labeled sodium molybdate. For swine this ratio was found to be about 5.

On the other hand, in ponies, cattle and sheep, the molybdenum fecal excretion is generally at least as much, if not more, than the urinary molybdenum excretion.

For humans the picture is very similar to that for rats and guinea pigs. The urinary output of molybdenum is almost always higher than the fecal molybdenum output, and is generally 60% to 80% of the total.

It is important to note that, whereas balance studies for humans are done without adding molybdenum to the diet, animal studies generally involve the addition of soluble molybdenum salts. Therefore, the bioavailability of molybdenum in normal human diets, compared to that of molybdenum in water as molybdate, is not known. Studies of humans with various molybdenum exposures, either in the workplace or in their water supply, indicate an increase in urinary output with increased exposure. However, the fecal molybdenum excretion was not measured, and thus it is not known whether the ratio of urinary molybdenum excretion to fecal Mo excretion changed with exposure to soluble molybdenum compounds.

There does not appear to be a bioaccumulation of molybdenum in animal or human tissues. The data on tissue levels would indicate that a steady state situation is quickly reached with increased inputs of molybdenum and when the dose is withdrawn the tissue levels quickly diminish to normal values, if there are no renal problems.

Newborns appear to have lower molybdenum concentrations in their tissues than adults. From birth the molybdenum concentrations increase until age 20-60, depending on the organ, and then decline. However, autopsies of patients with severe renal dysfunction have indicated significant molybdenum accumulations in the liver.

Most data indicate that a balance between molybdenum intake and excretion exists for most species (except ruminants), including humans. When intake is changed the excretion rates adjust so that balance is again reached in a matter of days. Molybdenum is widely considered to be a necessary micronutrient and the estimated adequate and safe intake ranges from 0.1 to 0.3 mg/day for 7 to 10 year-olds to 0.15 to 0.5 mg/day for adults. Many diets in the human balance studies reported were within these ranges, those that were below these values showed a slight retention of molybdenum.

In conclusion, hexavalent molybdenum is rapidly and nearly totally (50% to 100%) absorbed by guinea pigs, rats, mice and humans. It moves quickly into the bloodstream and various tissues, notably the liver and kidney. That which is absorbed is rapidly and nearly totally excreted, mostly in urine. Thus, the kidneys provide a strong homeostatic defense. The rates of absorption and excretion and patterns of distribution for humans are reasonably similar to those of rats and guinea pigs, perhaps less similar to mice and pigs, and not very similar to horses, cattle and sheep. While the absorption in humans appears to be less than that by rats and guinea pigs, the animal studies were done with the addition of soluble salts. The form of the molybdenum in the human diets is unknown.

IV. Human Exposure

Humans may be exposed to chemicals such as molybdenum from a variety of sources, including drinking water, food, ambient air, occupational settings and consumer products. This analysis of human exposure to molybdenum is limited to drinking water, food and ambient air because those media are considered to be sources common to all individuals. Even in limiting the analysis to these three sources, it must be recognized that individual exposure will vary widely based on many personal choices and on several factors over which there is little control. Where one lives, works and travels, what one eats and physiologic characteristics related to age, sex and health status can all profoundly affect daily exposure and intake. Individuals living in the same neighborhood or even in the same household can experience vastly different exposure patterns.

The information available on the range of human exposure and intake for molybdenum from drinking water, food and ambient air for the 70-kg adult male is presented in this Section. It is not possible to provide an estimate of the number of individuals experiencing specific combined exposures from those three sources. However, the summary of this Section provides some insight into the relative contributions of the three sources, especially drinking water, to the range of intake values suggested by the available data.

A. Exposure Estimation

1. Drinking Water

Limited information was obtained on the occurrence of molybdenum in drinking water. None of the Federal surveys included molybdenum as an analyte. However, information on several national surveys and one local survey was reviewed in Ciccone and Associates (1983). Detection limits for these studies were not reported.

In a study by Greathouse and Craun (1978, as cited in Ciccone and Associates 1983), 3,834 distribution water samples (from as many sites) were analyzed for molybdenum. Molybdenum occurred in 30% of the distribution water samples; the mean concentration in all distribution water samples was 8.0 µg/L, with a range of 1.1 to 52.7 µg/L. The water source for the samples was not specified. Additionally, the system sizes were not reported though they were apparently randomly distributed to be representative of the United States population.

In a report of trace elements in water (Kopp 1969, as cited in Ciccone and Associates 1983), 380 finished water samples from surface water sources nationwide were analyzed for molybdenum. Molybdenum was found in 29.9% of the samples, with a mean concentration for the positive values of 85.9 µg/L and a range of 3 to 1,024 µg/L.

Durfor and Becker (1962, as cited in Ciccone and Associates 1983), analyzed water samples from municipal water treatment facilities with variable water sources for molybdenum. Samples were taken from supplies in the 100 largest U.S. cities (according to the 1960 U.S. census). The median concentration of molybdenum was 1.4 µg/L; molybdenum concentrations ranged from not detected to 68 µg/L. The number of samples and the types of water analyzed were not reported.

In a local study of the Denver, Colorado municipal water supply (Barnett et al. 1969, as cited in Ciccone and Associates 1983), molybdenum was analyzed over a five-month period. The sources of water for the plant were lakes in the mining region. One sample was collected each month from 20 surface water sites and five groundwater sites, resulting in the analysis of 100 finished surface water samples and 25 finished groundwater samples. Mean concentrations of molybdenum in the surface water and groundwater samples were 39.85 µg/L (range of 1 to 240 µg/L) and 32.2 µg/L (range of 10 to 85 µg/L), respectively.

The levels of molybdenum observed in drinking water vary greatly in the studies obtained. Assuming that molybdenum is present at the highest concentration reported, i.e., 1,024 µg/L in the Kopp study, the daily intake for the 70-kg adult male consuming 2 liters of drinking water per day would be 2,048 µg/day or 29 µg/kg/day.

2. Diet

Molybdenum is considered an essential trace element in humans. The National Academy of Sciences (NAS) reports that the molybdenum content of food varies greatly. Legumes, cereal grains, leafy vegetables, fish, meats, liver and kidney are particularly rich in molybdenum (NAS); fruits, root and stem vegetables, dairy products, sugars, oils and fats contain much smaller quantities of this chemical (NAS 1977, Schroeder et al. 1970). Schroeder et al. (1970) also found that spinach, yam, canned soup, syrups, cocoa, mustard, wheat germ and sunflower seeds contain relatively large amounts of molybdenum.

Several studies have been conducted on the dietary intake of molybdenum. Tipton et al. (1966, as cited in NAS 1977) calculated the total dietary intake of molybdenum to be approximately 100 μg/day, and Hadjimarkos (1967, as cited in NAS 1977) estimated the human intake of molybdenum in food at 1,000 μg/day. Jacobson and Webster (1977, as cited in NAS 1980a) stated that typical hospital diets provided from 44 to 1,000 μg of molybdenum per day. Schroeder et al. (1970) estimated the daily intake of molybdenum in standard diets to range from 210 to 460 μg/day, with an average of 335 μg/day.

The above studies indicate that daily intakes of molybdenum in the United States range from 44 to 1,000 μg/day. As Friberg et al. (1975) indicated, a diet based primarily on leafy vegetables and legumes would result in a much higher intake of molybdenum than a diet based mainly on meat products. Based on the data presented above, NAS has estimated the daily dietary intake of molybdenum to be 100 µg/day for adults (NAS 1977), which would be equivalent to 1.4 µg/kg/day for a 70-kg adult male.

3. Air

Very limited information was obtained on the presence of molybdenum in ambient air. The U.S. Environmental Protection Agency's Environmental Monitoring Systems Laboratory provided information from a nationwide study on molybdenum concentrations in ambient air. The data obtained from the study includes samples that were collected and analyzed from 424 sites in 49 states, the District of Columbia, Puerto Rico and the Virgin Islands for the years 1977-1983 (USEPA 1984). Out of a total of 23,716 samples, concentrations of molybdenum in the air samples had an overall range of 0.002 to 0.442 $\mu g/m^3$, with a range of median and mean values by city and by year of 0.002 to 0.032 $\mu g/m^3$ and 0.0008 to 0.076 $\mu g/m^3$, respectively.

B. Summary

Table IV-1 presents a general view of the total amount of molybdenum received by a 70-kg adult male from ambient air, food and drinking water. Five separate exposure levels in drinking water, one exposure level in foods, and one exposure level from ambient air are shown in the table.

The data presented have been selected from an infinite number of possible combinations of concentrations for the three sources. Whether

Table IV-1 Estimated Intake of Molybdenum from the Environment by Adult Males

Concentration in Drinking Water (μg/L)	Estimated total intake in μg/kg/day from drinking water, food and air (% from drinking water):
0.0	1.4 (0)
1.0	1.4 (2)
10	1.7 (17)
100	4.3 (67)
1,000	30 (95)

Intake from each source:

Water: 1.0 μg/L: 0.029 μg/kg/day
10 μg/L: 0.29 μg/kg/day
100 μg/L: 2.9 μg/kg/day
1,000 μg/L: 29 μg/kg/day

Air: 0.032 $\mu g/m^3$: 0.011 μg/kg/day

Food: 100 μg/day: 1.4 μg/kg/day

exposure occurs at any specific combination of levels is not known; nor is it possible to determine the number of persons that would be exposed to molybdenum at any of the combined exposure levels. The data presented represent possible exposures based on the occurrence data and the estimated intakes.

The drinking water levels selected are representative of the range of levels observed in the studies obtained. It is assumed that the 70-kg adult male consumes 2 liters of drinking water per day.

The dietary molybdenum intake level was selected from the NAS estimate of molybdenum in the dry diet of adults as 100 µg/day (see 2. Diet).

The ambient air intake level was determined by using the high value of the range of median levels reported in ambient air (see 3. Air). There was essentially no difference in the contribution of ambient air to total exposure from molybdenum by calculating total intake using the low value of the range of median levels. It is assumed here that the average adult male inhales 23 m^3 of air per day (ICRP 1975). Assuming an intake of 0.011 µg/kg/day from air and the food intake of 100 µg/day, drinking water would be the predominant source of molybdenum exposure in the adult male when drinking water levels exceed approximately 49 µg/L.

An accurate assessment of the number of individuals for which drinking water is the predominant source of exposure cannot be determined from the data since specific locations containing high concentrations of molybdenum in drinking water and low concentrations of molybdenum in ambient air and food are unknown.

The relative source contribution data are based on estimated intake and do not account for a possible differential absorption rate for molybdenum by route of exposure. In addition, the effects of the chemical on the body may vary by different routes of exposure.

V. HEALTH EFFECTS IN ANIMALS

A. Acute Toxicity

In Section III.B. an experiment by Fairhall et al. (1945) was described. They administered four forms of molybdenum (molybdenite, molybdenum trioxide, calcium molybdate and ammonium molybdate) to white rats (sex and strain unspecified) in amounts ranging up to 500 mg Mo per day. The authors reported zero mortality for all doses of molybdenite. They reported 50% mortality for the lowest doses of the other compounds and 100% for the highest doses. The control group had a 15% mortality over the study period. The LD_{50} values calculated by the authors are given in Table V-1.

The authors also described an experiment in which guinea pigs were injected with molybdenum compounds in solution or suspension in 2 mL of isotonic chloride solution. The strain, sex and age of the animals was not given. The mortalities after four days, four weeks and four months are shown in Table V-2.

A dose of 200 mg Mo (as ammonium molybdate) caused a slowing of respiration. Some animals became cyanotic and all went into convulsions. The authors noted that the salt is strongly acidic. Moreover, there is the possibility that the ammonium ion might be responsible for the toxicity. A second group of animals that received one-tenth the amount showed no apparent effects. The majority of the deaths from injected MoO_3 occurred within two hours. X-Ray photographs of some of the guinea pigs one week after injection with calcium

Table V-1 LD_{50} Values for Ingestion of Molybdenum Compounds by White Rats[a]

Compound	LD_{50} mg Mo/kg/day	LD_{50} mg Mo/day
Molybdenum Trioxide	125	10
Calcium Molybdate[b]	101	15
Ammonium Molybdate	333	27

[a] Period of exposure ranged from 8 to 232 days.
[b] Rats receiving calcium molybdate weighed nearly twice as much as rats receiving other compounds.

Adapted from Fairhall et al. (1945).

Table V-2 Mortalities Resulting from the Intraperitoneal Injection of Molybdenum Compounds (Guinea Pigs)

Molybdenum compounds	Amount injected mg Mo	Amount injected mg Mo/kg	No. of Animals	Mortality (%) 4 days	Mortality (%) 4 weeks	Mortality (%) 4 months	Time on test of surviving animals (months)
Molybdenite	200	800	12	17	17	25	12
Molybdenum trioxide	100	400	8	75	75	75	12
Ammonium molybdate	20	80	8	0	0	0	12
Ammonium molybdate	200	800	12	100	--	--	--
Calcium molybdate	100	400	6	0	0	17	12

Adapted from Fairhall et al. (1945).

molybdate or molybdenite showed sharply defined masses in the peritoneal cavity. The authors noted that both calcium molybdate and molybdenite are quite insoluble. No similar masses were seen in the guinea pigs surviving MoO_3 injection.

Pham-Huu-Chanh (1965) described an experiment in which the toxicity of sodium molybdate was compared with that of sodium chromate, tungstate and metavanadate. This work was performed using male adult rabbits (Oryctolagus cuniculus L. Bourgogne stock). The mean weight was 2.50 ± 0.50 kg. The animals were divided into two groups for each salt (the number of animals in each group or the total is not specified). One group was anesthetized with urethane (1 g/kg intraperitoneally), the other was non-anesthetized. Arterial pressure was recorded from the right carotid artery; respiratory movements were followed by recording the endotracheal pressure. The sodium molybdate was administered in a physiological saline at a concentration of 100 mM/100 mL by slow continual perfusion into the femoral vein at a rate such that death took place in 60 ± 10 minutes. The lethal dose in 60 ± 10 minutes was calculated by the author to be 121 ± 53.7 mg Mo/kg.

The lethal dose for sodium molybdate was slightly larger than that of sodium chromate (which was 96.7 ± 13.5 mg Cr/kg). Both salts produced similar effects. Agitation and intense muscular tremor appeared 30 to 45 minutes after the beginning of the perfusions in the conscious rabbit. The animals were dyspneic and squealed. A general tonic contraction was reported to precede respiratory arrest.

Fairhall et al. (1945) also described an experiment conducted with guinea pigs that studied histopathological changes in animals following exposure to MoO_3. The number, strain and sex of the animals were not specified. Their weight was given as "about 200 g." The animals received (by stomach tube) uniform doses of 25, 50, 75, 100 or 200 mg Mo daily (or 125, 250, 375, 500 or 1,000 mg Mo/kg). At the two higher dose levels, all animals were dead by the 9th day. At the 250 and 375 mg Mo/kg doses the surviving half of the animals were killed on the 14th day and most of the animals of the lowest dosage level survived to the 25th day. Animals showing post-mortem changes were discarded (primarily animals that died during the night).

Histological examination of 32 animals in the higher exposure groups revealed marked fatty changes in the livers and kidneys. Focal necrosis and granuloma formation increased with increasing dose, so that at the highest dose nearly all animals showed some phase of this process.

In about half of the animals the lungs showed slight to moderate congestion. Adrenal cortical cells were usually more vacuolated in the low dosage groups (where survival times were longer), than in the higher exposure groups. The spleens in all the guinea pigs in the three lowest exposure groups and about one half those in each of the two highest exposure groups showed an apparent increase in pulp reticulum cells. The heart showed no significant histopathologic change.

Bandyopadhyay et al. (1981) investigated the effect of molybdenum and high protein on the livers and kidneys in rats. Male albino rats (Wistar strain from CIBA, Bombay) weighing 60 to 70 g were divided into four groups of five each. The first group served as a control and was given a basal diet with 10% protein (as casein). The second group received the basal diet plus 245 mg Mo/kg/day as ammonium molybdate dissolved in water. The third group received a high protein (20%) diet. The fourth group received the high protein diet with the same molybdenum intake as group 2. The rats were weighed biweekly. The experimental period lasted 28 days after which the animals were killed and tissues taken for analysis.

Histological examination of the livers of animals in group 2 showed that the orientation of the cells in cords was lost and also the structure and contents of the nuclei were altered. The size of the mast cells, intercellular spaces and diameter of the central veins were increased. Basophilic substances in the cytoplasm of the cells were also significantly increased. Histological examination of the livers from animals in group 4, however, were fairly normal. While the mast cells of group 4 were swollen, the swelling was less than that for group 2. No basophilic substances were observed for group 4.

Histological examination of kidney tissues of group 2 showed degenerative changes that were more marked than in the liver tissues. Positions of the nuclei of the tubular cells were not normal in many cells and the cytoplasm of the tubular cells appeared to be vacuolated. Furthermore, there was a dramatic increase in the lumen of the tubules. The cytoplasm of the tubular cells of group 4 were slightly less vacuolated than for group 2, but otherwise the kidneys of group 4 and group 2 were similar.

The authors noted a marked growth reduction in group 2 that was partially reversed in group 4 (by about a factor of 2). The activity of L-gulonolactone oxidase in the post-mitochondrial supernatant fraction of liver extract was decreased in group 2 ($P<0.001$). There was also a statistically significant decrease in the activity of alkaline phosphatase in liver lysosome in group 2 (compared to group 1). Acid phosphatase activities were stimulated in all fractions of the liver and kidney tissues of group 2. Succinic dehydrogenase (SDH) activity was also inhibited in group 2 compared to group 1 ($P<0.001$). It is possible that the ammonium ion was responsible for some of the toxicity.

Arrington and Davis (1953) studied the toxicity of molybdenum in rabbits. They used 40 Dutch rabbits of both sexes and different ages. Nine rabbits served as controls and 31 were fed sodium molybdate added to their ration as 140, 500, 1,000, 2,000 and 4,000 mg Mo/kg. The basal ration contained 2.7 mg Mo/kg and 16.4 mg Cu/kg. The molybdenum and copper analyses were done by the thiocyanate and carbamate methods, respectively. The molybdenum was added to the ration pellets by spraying an aqueous solution of the salt. The animals were examined daily for gross symptoms of toxicity and growth data were collected from weekly weights of 24 weanling rabbits placed on the experiment at six weeks of age.

Rabbits fed 1,000 mg Mo/kg in their diet (30 mg Mo/kg/day assuming an average weight of 2 kg and a daily food consumption of 60 g) or more developed a toxic syndrome characterized by anorexia, weight loss, alopecia, slight dermatosis, anemia and death. All of the animals, both mature and weanling, on the 4,000 mg Mo/kg diet (or 120 mg Mo/kg/day) died, with an average survival of 30 days for weanling rabbits and 51 days for mature rabbits. Eighty percent of the weanling and sixty-seven percent of the mature animals on the 2,000 mg Mo/kg (60 mg Mo/kg/day) diet died.

Alopecia was common in affected rabbits and was accompanied by slight dermatosis with rough, dry, scaly skin. There was a complete loss of hair over various portions of the body.

A deformity of the front legs, first noticed as an apparent soreness or weakness, occurred in 7 of the 11 young rabbits that exhibited other signs of toxicity. This progressed until the animals were unable to stand and their legs spread outward. While the ability to move the forelegs was not lost, they could not be maintained in the normal position. In three cases one or both feet bent inward at the carpus joint. In one rabbit severe bending and twisting of the humerus was observed.

The symptoms described above were accompanied by a decreased hemoglobin concentration and a decreased number of red blood cells. The first changes in these parameters were noticed at the same time as the gross signs of toxicity occurred. They continued to decrease until the animals died or were given copper therapy.

In addition to the experiment involving the 40 animals, two weanling rabbits were fed a ration containing 2,000 mg Mo/kg and 2,000 mg Cu/kg as copper sulfate (or 60 mg Mo/kg/day and 60 mg Cu/kg/day). These animals did not develop the disorders seen in the other test animals. Indeed, no abnormalities which could be related to molybdenum were seen over the experimental period of four months.

Three of the original group of 40 rabbits that received 1,000 mg Mo/kg (or 30 mg Mo/kg/day) were treated with copper when their condition was severe. The authors state that their deaths would have been probable. These animals returned to normal weight gains, normal blood composition and normal hair color in three weeks. However, the front leg deformity, which was present in two of the rabbits, responded only slightly to the copper treatment.

The investigators concluded that when 1,000 mg/kg or more molybdenum was fed to the rabbits, gross toxic symptoms were produced but supplementation of the diet with additional copper prevented the development of toxicity. In rabbits with severe toxic symptoms, the administration of copper resulted in rapid recovery.

Huber et al. (1971) studied the response of lactating dairy cows to high levels of dietary molybdenum. Two trials were conducted. Trial 1 involved four cows of unspecified age, weight and strain (Holstein cows were specified for Trial 2). For the first 180 days all cows were administered a ration of 11.4 kg of orchard grass hay and 5.5 kg of a concentrate which contained 6 mg/kg copper. The molybdenum content of the basal ration was not specified. Just prior to feeding, sodium molybdate was thoroughly mixed with the concentrate (100 mg/kg). Intake of molybdenum averaged 1.7 g/day for each animal. Assuming the cows weighed 500 kg this would be equivalent to 3.4 mg

Mo/kg/day. After two months on the diet two of the cows were randomly selected to receive additional sulfate at a level of 0.13% of the diet. Two months later that was increased to 0.26%.

None of the animals showed overt signs of toxicity after six months and the molybdenum intake was increased to 3.4 g/day or about 7 mg Mo/kg/day (200 mg/kg). One week later one of the cows receiving this dose and the supplemental sulfate developed severe diarrhea and exhibited signs of inanition, cessation of milk synthesis and general emaciation. This animal recovered rapidly when molybdenum and added sulfate were withdrawn, but once again exhibited signs of toxicity when the molybdenum and sulfate were replaced in the diet. Upon increasing the molybdenum dose to 5.1 g/day, or about 10 mg Mo/kg/day for three of the cows, two of them exhibited diarrhea and emaciation. The addition of 0.26% sulfate greatly increased the severity of molybdenum toxicity.

In trial 2, seven Holstein cows and one yearling heifer were placed on the basal ration. For the first two months of treatment, sodium molybdate was mixed with the concentrate to give a molybdenum content of 53 mg/kg. The cows received a daily ration of 6.8 kg of orchard grass and 4.5 kg of concentrate. Thus, they received about 600 mg Mo/day or 1.2 mg Mo/kg/day assuming a weight of 500 kg. The animals were divided into two groups of four. One group continued on the same regimen while the others had their molybdenum dose increased to 173 mg/kg (about 4 mg Mo/kg/day). No toxicity symptoms were noticed for the cows on 53 mg/kg, but one cow developed severe diarrhea two months after receiving the higher dose. Body weight gains averaged 0.44 kg/day less for the high molybdenum group compared to the low molybdenum group over three months.

At the end of the six month study period, the animals were sacrificed and tissue samples were analyzed for copper and molybdenum content. The authors observed that copper in the kidney and brain was increased, while that in the liver was decreased. The kidney and spleen were found to concentrate molybdenum to a greater degree than the liver or other organs. The authors noted that all of the animals were on a low copper intake at 6 mg/kg (dry weight) in their diet. Thus, these animals cannot be assumed to have responded as an animal on a normal diet would respond.

In another experiment, Campbell et al. (1976) used 24 bull calves, three to five months old, and of unreported strain, in a feeding trial in which the levels and ratios of copper and molybdenum were varied. The basal diet containing 1.29 mg Mo/kg and 8 mg Cu/kg was fed to all groups. The animals in group II had their diet supplemented with sodium molybdate and copper sulfate, added to the diet to give a dietary intake of 342 mg Cu/kg and 53 mg Mo/kg. Groups I and II received these diets for the entire study period of 98 days. Group III had the basal diet supplemented with sodium molybdate and copper sulfate to yield 11 mg Cu/kg and 295 mg Mo/kg for the first 42 days (Phase I), and then the copper and molybdenum concentrations were changed to 342 mg/kg and 53 mg/kg, respectively (Phase II). The animals were weighed weekly and hemicastrated at the end of the first 42 days (Phase I). The remaining testicle was removed at the end of the next 56 days (Phase II). Blood and hair samples were collected at the beginning and end of Phase I.

Unfortunately, the dietary intake of food was not measured. The initial and final weights for Phase I for groups I, II, and III were 93 and 128 kg, 88 and 126 kg and 80 and 73 kg, respectively. Thus, the average weights for groups I, II and III during Phase I were 111, 107 and 77 kg, respectively. The average daily weight gain for group III was significantly ($P<0.01$) different from groups I and II during Phase I. Assuming that a 500 kg cow consumes 7,500 g of food per day and that this can be scaled down linearly, then 1 mg/kg in the food equals 0.015 mg/kg/day. Thus, the molybdenum doses for groups I, II and III during Phase I were 0.02 mg Mo/kg/day, 0.8 mg Mo/kg/day and 4.4 mg Mo/kg/day.

The animals in group III not only lost weight during Phase I, they also had severe diarrhea which brought about emaciation. In addition, it was noted that they had a yellowing of the skin in all exposed areas, sunken eyes, listlessness and a stiffening of the forelegs causing a posty gait. Nervousness, weakness and loss of appetite were noted as the study progressed. The molybdenum levels in hair for groups I, II and III were 9.7, 31.9 and 105.8 ppm Mo, respectively at the end of Phase I. Extreme nutritional stress was evident by 42 days and Phase I was terminated and the diet changed as noted. During Phase II the toxicity symptoms were reversed. No differences were noted for the blood parameters measured (hemoglobin, packed cell volume or percent plasma protein between groups).

Testicular growth and development as determined by weight and size was retarded during Phase I in animals in group III. Improvement in testicular development in group III occurred during Phase II.

Table V-3 summarizes the acute effects of molybdenum in animals.

B. Subchronic Toxicity

In the next two sections of this document, toxicity is divided into subchronic and chronic toxicity. Subchronic refers to studies which involve less than a year exposure and only one generation. Chronic refers to studies involving more than a year or more than one generation.

Jeter and Davis (1954) studied the effects of dietary molybdenum on growth, hemoglobin, reproduction and lactation of Long-Evans rats of both sexes. The animals were housed in wire cages and fed a basal diet of a mineralized milk-sucrose mixture containing 1.78 mg Cu/kg and <1 mg Mo/kg. Copper and molybdenum were added in various levels as copper sulfate and sodium molybdate. Distilled water was supplied.

The rats were weighed weekly from weaning to 11 weeks of age and hemoglobin was determined at 4, 7, 10 and 13 weeks of age. Fertility studies were initiated at the completion of the growth experiments. These involved mating of the experimental males and females. In cases of apparent infertility, the rats were bred to proved fertile rats on a stock diet. Histological sections

Table V-3 Summary of Acute Effects of Molybdenum in Animals

Reference	Species	Form	Route	Dose	Mortality data	Other effects
Fairhall et al. (1945)	Rat	MoO_3	Food	125^a	LD_{50}	
		$CaMoO_4$		101^a	LD_{50}	
		$(NH_4)_2MoO_4$		330^a	LD_{50}	
	Guinea Pig	$(NH_4)_2MoO_4$	IP	800^b		Dec. respiration, cyanosis
				80^b		No effect
	Guinea Pig	MoO_3	Stom. Tube	125^b	Survival	
				$250-375^b$	50% at 14 days	
				$500-1,000^b$	100% (9 days)	Liver, kidney, lung damage
Pham-Huu-Chanh (1965)	Rabbit	Na_2MoO_4	IV Drip	121^b	100% (60 min)	Agitation, tremors
Bandyopadhyay et al. (1981)	Rat	$(NH_4)_2MoO_4$	H_2O	245^a		Decreased growth, liver, kidney, pathology
Arrington and Davis (1953)	Rabbit	Na_2MoO_4	Diet	$0-15^a$		No effect
				30^a		Anemia, alopecia, bone abnormalities
				60^a	67-80%	Weight loss, anemia, alopecia, dermatosis, bone abnormalities
				120^a	100% (30-50 days)	Anemia, weight loss, bone abnormalities
Huber et al. (1971)	Cow	Na_2MoO_4	Diet	$1.2-3.4^a$		No symptoms
				$4-10^a$		Diarrhea, decreased wt. gain
Campbell et al. (1976)	Cow	Na_2MoO_4	Diet	4.4^a		Weight loss, diarrhea, decreased testicular development

[a] Expressed as mg/kg/day.
[b] Expressed as mg/kg.

were made of the testes. Gestation and lactation performance were determined by the number of litters, size and weight of litter, loss of weight of lactating females and weight of litter at weaning. Newborn litters were reduced to six when they exceeded that figure. Initial weights were not reported.

The growth data are summarized in Table V-4. The growth of male rats was retarded at 2, 8, and 14 mg Mo/kg/day at the lower copper level (0.5 mg Cu/kg/day) while the growth of females was retarded only at the two higher molybdenum levels.

The authors reported that hemoglobin concentrations were not affected by any diet. Achromotrichia followed by varying degrees of alopecia was observed in some but not all of the rats in the groups receiving 80 and 140 mg/kg of molybdenum. Depigmentation was occasionally observed in rats receiving 20 mg Mo/kg (2 mg Mo/kg/day).

While there was no indication of female infertility, only 25% of the male rats which received 80 and 140 mg/kg (8 and 14 mg Mo/kg/day) proved to be fertile. Histological examination of the testes from these males showed various degrees of seminiferous tubule degeneration, while the testes from rats receiving less than 1 mg/kg (<0.1 mg Mo/kg/day) were normal.

There was no detrimental effect on gestation. Four females fed a ration of 700 mg Mo/kg (70 mg Mo/kg/day) for ten days (the authors did not

Table V-4 Growth of Rats Receiving Various Amounts of Mo and Cu in Diet

Ration				
Mo mg/kg	Cu mg/kg	No. & sex of rats	Average gain at 11 weeks, g	Mo dose (mg Mo/kg/day)[a]
<1	20	4 M	163	<0.1
		4 F		
80	20	4 M	135	8
		4 F		
<1	5	8 M	176	<0.1
		8 F	128	
20	5	4 M	140[b]	2
		4 F	117	
80	5	8 M	147[b]	8
		8 F	105[b]	
140	5	4 M	80[c]	14
		4 F	85[b]	

[a] Estimated assuming average weight of 0.1 kg and 10 g/day food consumption.
[b] Growth retardation significant at 5% level.
[c] Growth retardation significant at 1% level.

Adapted from Jeter and Davis (1954).

specify copper concentrations) showed irregular estrus cycles over a five-week period. Similar rats on the same ration with no added molybdenum had normal estrus.

The lactation performance indicated a reduced milk yield from rats consuming diets with added molybdenum. However, it is possible that there was increased secretion of molybdenum into the milk and that this might account for the low weaning weights of the litters.

Gray and Daniel (1964) investigated the effects of molybdenum added to the diets of both copper-deficient and copper-adequate rats and the interactions with copper and sulfate. Weanling male Sprague-Dawley rats were used. Copper-depleted animals were obtained by weaning at 21 days of age and feeding on unsupplemented whole milk powder. At the beginning of the experiment the animals were randomized into groups of six animals each according to weight and length of depletion period.

Copper-deficient animals were fed a basal diet containing <1 mg Cu/kg. Copper-adequate animals were fed the same diet supplemented with 5.33 mg Cu/kg (as copper sulfate). Molybdenum was added as sodium molybdate and sulfate was added as sodium sulfate. Weights were recorded weekly. Hemoglobin determinations were made at the end of the depletion period for the depleted rats and at the end of the experimental period for all animals.

The authors demonstrated that copper-adequate rats fed 800 mg Mo/kg (or 80 mg Mo/kg/day, assuming an average weight of 100 g and food consumption of 10 g/day) showed a significant reduction in growth (a weight gain of 1/2 of controls) over the four-week experimental period. There was no effect on hemoglobin. No other toxic effects were reported. When sulfate was added at at a concentration of 645 mg/kg (64.5 mg SO_4/kg/day) or higher along with 800 mg Mo/kg, growth reduction did not occur. When either 1% DL-methionine or 300 mg Cu/kg were added to the diet, the toxic effect of molybdenum on growth was still present but somewhat reduced.

When copper-depleted rats (these animals were depleted for 16 to 17 days and then fed the copper-deficient basal diet for the four-week experimental period) were given either 10 or 100 mg Mo/kg in the diet (corresponding to 1 or 10 mg Mo/kg/day), a significant effect at both molybdenum levels upon growth was observed. Weight gains of 2/3 and 1/3 of those for the control were observed for 10 and 100 mg Mo/kg, respectively. Moreover, a decrease ($P<0.05$) in hemoglobin concentration was observed for the animals receiving 100 mg/kg (10 mg Mo/kg/day). Diarrhea was common in the molybdenum-intoxicated rats. In these copper-deficient animals, when 2.7% sulfate was added, the effect of molybdenum on growth at 10 mg Mo/kg (1 mg Mo/kg/day) was exacerbated. At 100 mg Mo/kg (10 mg Mo/kg/day) all rats died when 2.7% sulfate was added. When 300 mg Cu/kg was added, the toxic effects of molybdenum and molybdenum plus sulfate disappeared.

The authors reported that copper concentrations in the liver of the copper-adequate animals were significantly ($P<0.01$) increased when they received 800 mg Mo/kg (80 mg Mo/kg/day) in their diets. This effect was reversed when the animals received additional copper or sulfate. For the copper-deficient animals, the liver-copper levels were low and were not affected by the addition of molybdenum in the diet.

Ostrom et al. (1961) studied the effect of molybdenum on connective tissue in rats. Albino rats of the NMRI-D strain (sex unspecified, 21 days old, weighing 29 to 51 g) were placed in individual cages. The rats were divided into two groups, a control group on a basal diet (concentration of molybdenum and copper unreported) and a test group with the basal diet supplemented with 400 mg Mo/kg as sodium molybdate. The period of the experiment was five weeks.

At the end of five weeks the control group (four rats) had a mean weight of 160 g in comparison to 109 g for the test group. Assuming an average weight of 75 g for the test group (growth was nearly linear) and an average food consumption of 10 g/day, the dose level for the test group was about 50 mg Mo/kg/day.

At the termination of the experimental period the animals were sacrificed. Blood samples were obtained and each animal was examined for mandibular and maxillary exostoses. Ten of the twenty rats in the test group developed mandibular exostoses. These ten rats also had the poorest weight gains and had hemoglobin concentrations that were 61% of control, whereas the ten test-group rats without exostoses had approximately the same hemoglobin concentrations as the control rats and an average weight gain that was 83% of the controls. The average hematocrit values for the exostoses subgroup were about 62% of those for the controls. All groups had similar white blood cell counts. Histological examination of the mandibles and teeth revealed morphological changes similar to lathyrism.

Miller et al. (1956) fed albino rats (Holtzman strain) varying amounts of molybdenum and sulfate. Twenty-four rats (equal numbers of each sex, 21 days old, weighing 35 to 50 g) were used in these studies. Rats of each sex were randomly assigned into six different treatment groups. The basal diet contained 4 mg Cu/kg and less than 0.2 mg Mo/kg. Molybdenum was added at 75 mg/kg and 300 mg/kg. This corresponds to 7.5 and 30 mg Mo/kg/day if an average weight of 100 g and food consumption of 10 g/day is assumed. Three groups of rats also received a supplement of 2,200 mg/kg sulfate (as a 1:1 mixture of sodium and potassium sulfate). All rats were sacrificed after six weeks. Blood samples were obtained as well as samples of liver tissue. The authors reported that molybdenum alone exerted a significant (P value not reported) growth inhibition at the 75 and 300 mg/kg level (a reduction of weight gain by 40% and 78%, respectively). The addition of sulfate reversed this inhibition at 75 mg Mo/kg and reduced it at 300 mg/kg. The addition of molybdenum alone increased liver copper and molybdenum concentrations. These increases were reduced by sulfate supplementation.

An enlargement of the femoro-tibial joint and a thickening of the epiphysis of the femur and tibia were observed in the rats receiving 75 and

300 mg Mo/kg without sulfate, and 300 mg Mo/kg with sulfate. Histological examination of the femurs indicated a chrono-dystrophy of the epiphysial cartilages. The femurs in the other groups were normal.

Cox et al. (1960) studied the effect of excess dietary molybdenum on rat liver and heart enzymes. Weanling piebald rats (Long-Evans), 21 to 25 days old were divided randomly by sex and weight into three treatment groups. They were maintained on a mineralized whole milk diet to which had been added 0, 500, or 800 mg Mo/kg as sodium molybdate. The copper content of the diet was 7.5 mg/kg. The period of study was five weeks for the males and eight weeks for the females. The number and weight of the rats were not given. Assuming an average weight of 100 g and food consumption of 10 g/day, the doses administered would be 0, 50 or 80 mg Mo/kg/day.

The authors observed that the animals on the 50 and 80 mg Mo/kg/day diets exhibited a decreased growth rate, marked diarrhea and emaciation. Reduced liver xanthine oxidase activity ($P<0.05$) and liver respiration ($P<0.01$) for both diets was observed. The reduction of xanthine oxidase activity is of interest because Koval'skiy et al. (1961) reported increased levels of xanthine oxidase in tissues of humans exposed to high levels of molybdenum.

Arthur (1965) studied the effect of excess dietary molybdenum (added as sodium molybdate) on guinea pigs of unspecified strain. Five experiments were conducted. In all but the first experiment, the animals were weanlings weighing 250 to 350 g. In the first experiment, the guinea pigs weighed 300 to 400 g. Both sexes were used and the animals were randomly selected for each diet.

The animals were reared in an air-conditioned room and given feed and water *ad libitum*. The basal diet used in the first two experiments contained 8.9 mg Cu/kg, 0.3 mg Mo/kg and 0.25% sulfate. The basal diet for experiments 3, 4 and 5 contained 5.6 mg Cu/kg, 1.8 mg Mo/kg and 0.13% sulfate.

The first experiment involved five guinea pigs on each diet. Animals were maintained for eight weeks on diets with molybdenum content ranging from the basal diet to 8,000 mg/kg in increments of 1,000 mg/kg. The authors do not give data on food intake. Assuming a guinea pig weighing 0.75 kg consumes 30 g of food each day, and scaling linearly, 1 mg/kg in the food = 0.04 mg/kg/day. Thus, 8,000 mg/kg = 320 mg Mo/kg/day.

The authors reported that weight gains decreased with added molybdenum from 1,000 to 4,000 mg/kg (40 to 160 mg Mo/kg/day). Losses of weight occurred above 4,000 mg/kg (160 mg Mo/kg/day). The color of the hair of the black guinea pigs changed to grey when the dose was above 1,000 mg/kg (40 mg Mo/kg/day). The authors reported this phenomena was observed under similar conditions in red and brown guinea pigs. Some fatalities were reported with an increasing occurrence at doses larger than 5,000 mg/kg (200 mg Mo/kg/day). Approximately 3/4 of the animals receiving from 6,000 to 8,000 mg/kg (240 to 320 mg Mo/kg/day) died.

In Experiment 2 the levels of copper and molybdenum were both varied with either 0, 10 or 20 mg Cu/kg (as copper sulfate) and 0 or 2,000 mg Mo/kg added to the diet. There were ten colored animals assigned to each diet. All of the animals whose diets contained 2,000 mg/kg added molybdenum (80 mg Mo/kg/day) and either 0 or 10 mg/kg added copper (0.4 mg Cu/kg/day) developed grey hair. The inclusion of 20 mg Cu/kg, however, overcame this effect. All animals on added molybdenum accumulated molybdenum in the liver. The animals on 2,000 mg Mo/kg had a smaller weight gain that was only partially alleviated by the additional copper.

In a third experiment, three weanling guinea pigs were supplied a low copper basal diet (5.6 mg Cu/kg and 1.8 mg Mo/kg) with additions of 0, 200, 500, 1,000 or 2,000 mg Mo/kg. There was an increase in molybdenum in the blood, liver and kidney with increasing dietary molybdenum levels. There was an increase in copper in the blood and kidney with increasing molybdenum intake, but at 1,000 and 2,000 mg Mo/kg (40 and 80 mg Mo/kg/day), there was a decrease in liver copper concentrations.

Suttle (1974) studied the effect of molybdenum supplements in the diet on the utilization of dietary copper by guinea pigs. The liver copper stores of four groups of six male albino guinea pigs weighing about 500 g (no further description given) were depleted by feeding a copper-deficient diet (2 mg Cu/kg). They were then repleted on a diet containing 8 mg Cu/kg and 0.6 mg Mo/kg. Molybdenum, as ammonium molybdate, was added to four of the diets to provide 0.6, 4.1, 26.0 and 104 mg Mo/kg. The author estimated a daily food consumption of 35 g. Thus, for a 500 g animal, 1 mg/kg in the diet would correspond to 0.07 mg/kg/day. The four dietary intakes above would correspond to 0.04, 0.3, 1.8 and 7.3 mg Mo/kg/day.

The animals were repleted for 14 days and the increase in liver copper after the repletion period was obtained by comparison with an initial slaughter group. The initial slaughter group had a value of 25.3 ± 3.9 mg Cu/kg (dry weight) in their livers (mean ± standard error). The copper-repleted guinea pigs had 85.3 ± 3.8, 71.6 ± 6.6, 57.6 ± 5.9 and 38.3 ± 4.0 ppm Cu in their livers for the groups receiving 0.04, 0.3, 1.8 and 7.3 mg Mo/kg/day, respectively. Total plasma copper increased from 0.468 ± 0.043 mg Cu/L to 3.877 ± 0.221 mg Cu/L from the lowest to highest molybdenum group. None of this increase was attributable to an increase in ceruloplasmin copper. The authors concluded that the additional molybdenum significantly impaired the utilization of dietary copper.

Widjajakusuma et al. (1973) evaluated the effect of the molybdate ion on thyroid function in rabbits. Fifty-six male New Zealand rabbits weighing 1.5 to 2.7 kg were housed singly, fed an oats-alfalfa mixture and treated with sulphaquinoxaline to prevent coccidiosis. On completion of the drug treatment the rabbits were placed in three experimental groups. Each of the three experiments had a control group and a test group. The test groups received 2,200 mg Mo/kg in their diet as sodium molybdate, while the control groups received an equivalent quantity of NaCl in place of sodium molybdate. In the first experiment the study period was 26 days (eight and seven animals in the control and test group, respectively). In the second experiment the test rabbits fed the molybdate diet for 31 days, were returned to the control diet (molybdenum and copper content of the control diet not specified) for ten days, then went back to the molybdenum diet for four days. There were seven controls and five test animals in Experiment 2. In Experiment 3, the period of study was 25 days and there were 11 and 8 animals in the control and test group, respectively. The test group received the molybdate diet as described in Experiment 1. In addition, there was a "food-restricted" control group of ten animals which received a quantity of the control diet equal to the quantity of molybdate diet consumed on the previous day by the test group.

Rabbits were examined daily for gross signs of molybdenum toxicity. Hemoglobin concentrations, packed cell values and body weights were recorded weekly. When severe (unspecified) molybdenosis was evident in approximately half the test rabbits, plasma T_4 concentrations were determined. Thyroxine secretion and T_4 distribution space were determined at the end of each experimental period. At the completion of Experiment 3, 24 thyroid glands were removed for histological studies.

The authors reported that molybdenosis was severe enough to kill some of the rabbits. The daily food consumption was not recorded. The average weights of the molybdate-fed animals in the three experiments at the end of the study periods were 1.833 ± 0.09, 1.941 ± 0.154 and 1.655 ± 0.113 kg, respectively. Assuming that a 2 kg rabbit consumes 60 g of food daily, 1 mg/kg of molybdenum in the food equals 0.03 mg Mo/kg/day. Thus, their dose was 66 mg Mo/kg/day.

The molybdate-fed rabbits all showed a significant reduction in growth compared to controls (P<0.01). In addition, the T_4 levels were lower in the test groups than in the controls. The T_4 levels of the food-restricted animals were also lower than controls (no P value). Thyroxine distribution space values remained at control levels for test animals except for Experiment 2 where it was more than twice as high for the test animals (P<0.001). Fractional degradation rates were not different for any pairs. Thyroxine secretion rates decreased by 38% to 51% in Experiments 1 and 3 in the test animals, but increased by 37% in Experiment 2.

Histological examination of thyroid tissue from the animals in Experiment 3 showed extensive changes in the follicular cells, luminal diameter and interfollicular connective tissue. Compared to controls, both the test group and the food-restricted group had thinner follicular epithelia and larger luminal compartments. However, the molybdate-fed animals had degenerative alterations in the follicular epithelia and interfollicular connective tissue not observed in the food-restricted group.

The authors concluded that molybdate at these levels caused thyroidal hypofunction, but that part of this was due to reduced food intake. However, some additional degeneration of the thyroid gland was attributed directly to molybdate.

Asmangulyan (1965) studied the effect of molybdenum in rabbits on weight gain, as well as, hemoglobin, erythrocytes and leukocytes in the blood and sulfhydryl (SH) groups in the blood serum. These parameters were measured three times before the experiment began and then performed each month during the experimental period.

Twenty rabbits of unspecified age, sex and strain were used. They were divided into five groups. The control group consisted of five animals. Four rabbits each received an oral dose of 50, 5 and 0.5 mg Mo/kg each day except Sunday. Three animals received a dose of 0.025 mg Mo/kg on the same schedule. The molybdenum was given as ammonium molybdate.

The experiment lasted six months. During this period the author reported that no gross symptoms were seen. He also reported that at 5 and 50 mg Mo/kg/day a growth retardation was observed (no data given). A marked increase in serum SH groups (roughly a two-fold increase) was measured in animals receiving 50 mg Mo/kg/day. Smaller increases were seen in the 5- and 0.5-mg Mo/kg/day dose groups. None was seen at 0.025 mg Mo/kg/day. Similar increases in SH groups in several organs were observed (particularly the liver and spleen) at the higher doses, but not at the lowest dose (0.025 mg Mo/kg/day). The author also found decreases in the vitamin C content of the kidney and liver in the higher dose group, but not in the lowest dose group.

In addition, the author reported several anomalies in various organs found in the histological examination of the highest dose group. These were present, but in a lesser degree in the 5-mg Mo/kg/day dose group.

Dale et al. (1973) studied the interaction of copper, molybdenum and sulfate in young swine. Forty-eight crossbred pigs (4 to 6 weeks old and averaging 9 kg) were used. Six groups of eight pigs were randomly allotted and administered various dietary treatments. Only two of those diets are of importance for this report. Diet 1, the basal diet, contained 11 mg Cu/kg (the molybdenum concentration was not specified). Diet 3 was the same as the basal diet but 50 mg Mo/kg was added as sodium molybdate. The other diets contained various mixtures with sodium sulfate added. The study period was 130 days. The daily food consumption was not reported. Assuming a 60-kg pig consumes 2,400 g/day, then 1 mg Mo/kg in the food corresponds to 0.04 mg Mo/kg/day. Assuming linearity, 50 mg Mo/kg in the diet is then equal to a dose of 2 mg Mo/kg/day.

There was no significant effect of molybdenum on growth rates at this dose. While hemoglobin decreased significantly (P value not given) at the fourth week in the high molybdenum group, that effect was transitory and not present at the end of the study period. Liver copper was significantly (no P value given) decreased in the high molybdenum group. The treatment group also had a significantly greater copper retention and urine volume than did the controls.

Kincaid (1980) added various levels of molybdenum (as ammonium molybdate) to the drinking water of calves in order to establish the minimum toxic concentration. Twelve male Holstein calves (five weeks old) were randomly assigned to four groups (three per group) which received 0, 1, 10 or 50 mg Mo/L added to their drinking water. The basal diet contained 13 mg Cu/kg, 0.29% sulfur and less than 1 mg Mo/kg. The daily water consumption ranged from 4.8 to 5.4 L and daily food consumption was 1.7 to 2.1 kg. The initial average weight of the calves was 66 kg and their average daily weight gain during the 21 day study was 0.71 kg. There were no significant differences in weight gains between the four groups. The average weight during the experimental period was 73 kg. The authors reported the average daily consumption of molybdenum in water (by way of food it was <2 mg/day) to be <1, 4.8, 50, and 270 mg, respectively for the 0-, 1-, 10- and 50-mg Mo/L groups. Thus the average daily doses were <0.01, 0.07, 0.7 or 3.7 mg Mo/kg/day, respectively.

As stated previously, there was no effect observed on growth of the calves nor on the acceptability of the water. Plasma copper was elevated significantly in those calves receiving the highest dose. The calculated percentage of copper as ceruloplasmin decreased from 61% to 43% with all additions of molybdenum, but these changes were not statistically significant. Thus, the increase in plasma copper in the highest dose group was as non-ceruloplasmin copper. Also, with 50 mg Mo/L in the water, the uptake of copper from plasma into the liver was less than the endogenous loss. Whereas at 10 mg Mo/L, the endogenous loss of copper by the liver was nearly equal to uptake. The ratios of copper to molybdenum in the dietary intakes of the four groups were calculated to be >27, 4.6, 0.5 and 0.08 for the 0, 1, 10 and 50 mg Mo/L groups, respectively. The authors suggested that the minimum level for toxicity of molybdenum in the drinking water of calves is between 10 and 50 mg Mo/L (0.7 to 3.7 mg Mo/kg/day).

The subchronic health effects of molybdenum in animals are summarized in Table V-5.

C. Chronic Toxicity

Winston (1973) described a study of the effect of cold stress on rats receiving moderately elevated levels of molybdenum in their drinking water. Sprague-Dawley rats of both sexes were used. The animals were 5 to 12 months old with the males weighing between 0.4 and 0.7 kg and the females 0.22 to 0.35 kg. They were divided into four groups. Each group had 11 to 12 males (45 males in all) and 2 to 5 females (12 females in all). Two of the groups served as controls, and were kept at 25°C throughout the experimental period of four days. One control group received a basal diet containing 1 to 3 mg Mo/kg for their entire lives. The other control group received the same basal diet but was also administered drinking water with a concentration of 10 mg Mo/L (as sodium molybdate) for their entire lives.

The other two groups had similar diets their entire lives, but were placed for four days in a cold room at 2°C to 3°C. The light/dark cycle was 12 hours. Weight changes and food intake were measured daily.

After four days it was observed that although females lost a smaller percentage of weight than the males, both males and females receiving 10 mg Mo/L in their drinking water for their entire lives lost nearly twice as

Table V-5 Summary of Subchronic Health Effects of Molybdenum in Animals

Reference	Species	Form	Route	Duration	Dose (mg Mo/kg/day)	Cu status	Effects
Jeter and Davis (1954)	Rat	Na_2MoO_4	Diet	13 wks	2-14	D[a]	Decreased growth
					8-14	A(?)[b]	Alopecia, male infertility
Gray and Daniel (1964)	Rat	Na_2MoO_4	Diet	4 wks	1	D	Decreased wt. gain
					10	D	Decreased wt. gain, decreased hemoglobin
					80	A[c]	Decreased wt. gain, increased liver Cu
Ostrom et al (1961)	Rat	Na_2MoO_4	Diet	5 wks	50	A(?)	Decreased growth, decreased hemoglobin, mandibular exostoses
Miller et al. (1956)	Rat	H_2MoO_4	Diet	6 wks	7.5-30	A	Decreased growth, increased liver Mo and Cu, bone abnormalities
Cox et al. (1960)	Rat	Na_2MoO_4	Diet	5-8 wks	50-80	A	Decreased growth, diarrhea
Arthur (1965)	Guinea Pig	Na_2MoO_4	Diet	8 wks	40-160	A	Decreased wt. gain, loss of hair color
					200-320	A	Wt. loss
Suttle (1974)	Guinea Pig	$(NH_4)_2MoO_4$	Diet	2 wks	0.04-7.3	D	Decreased uptake of Cu
Widjajakusuma et al.	Rabbit	Na_2MoO_4	Diet	26 days	66	A(?)	Decreased growth, decreased serum T_4, thyroid injury
Asmangulyan (1965)	Rabbit	$(NH_4)_2MoO_4$	Oral	6 mo	.5	A(?)	Increased serum-SH
					5-50		Increased serum-SH, decreased growth
Dale et al. (1973)	Pig	Na_2MoO_4	Diet	130 days	2	A	Decreased liver Cu, no decreased growth
Kincaid (1980)	Cow	$(NH_4)_2MoO_4$	Drinking Water	21 days	0.07-3.7	A	Increased plasma Cu, decreased liver Cu, no change in growth

[a] D = Copper deficiency in experimental animal created prior to molybdenum dosing.
[b] A(?) = Copper concentration not reported but assumed to be adequate.
[c] A = Copper concentration measured (ranged from 4 to 9 mg/kg) and assumed to be adequate.

much weight (approximately 13%) when placed in the cold room as those that had no added molybdenum in their drinking water. This difference was highly significant ($P<0.01$).

Water intake was not measured. Assuming a mature rat consumes about 20 mL per day, rats receiving 10 mg Mo/L would ingest about 0.2 mg Mo/day. Using the weight ranges supplied, this corresponds to doses of 0.3 to 0.5 mg Mo/kg/day for the males and 0.6 to 0.9 mg Mo/kg/day for the females. If it is assumed that water intake is proportional to body weight (as opposed to the assumption that all rats consume equal amounts of water), then a 0.4 kg rat consumes 20 mL/day of water containing 10 mg Mo/L would receive 0.4 mg Mo/kg/day, and this would hold for both males and females.

Schroeder and Mitchener (1971) studied the effects of several trace elements (including molybdenum) in the drinking water of mice. They used Charles River CD strain mice that had been born in a specially designed laboratory to minimize trace metal contamination. The diet contained 1.95 mg Cu/kg (wet weight) and 0.45 mg Mo/kg (wet weight). Five male-female pairs of animals were randomly selected from litters divided at the time of weaning. They were placed in separate cages, and supplied with drinking water containing 10 mg Mo/L (as molybdate, cation not specified). Water consumption rates were not reported. Assuming that a 20 g mouse would consume 3 g of water per day, 10 mg Mo/L in the water would be equivalent to 1.5 mg Mo/kg/day.

The mice were allowed to breed as often as they would up to six months of age. At weaning, pairs of pups were randomly selected from the first litter

(F_1A generation), the second litter (F_1B) and sometimes from the third (F_1C) and those were allowed to breed as they would to produce F_2 generations. Pairs were likewise selected at random from the F_2A litters and allowed to breed with the F_3A and sometimes with the F_3B generation. Control animals received plain deionized water and were treated similarly.

The parameters measured were the intervals between litters, the age at which the pair produced its first litter, the ratio of males to females, and the numbers of runts, deaths, stillborns, breeding failures and congenital abnormalities. There was an increased number of early deaths of the F_1 offspring ($P<0.001$), there was an increased number of early deaths in the F_3 generation offspring ($P<0.0001$). There were more maternal deaths ($P<0.05$) in the F_3 generation, more dead litters in the F_3 generation ($P<0.05$) and more runts in the F_3 generation ($P<0.0001$) than in the controls. The experiment was discontinued with the F_3C generation.

D. Other Effects

1. Carcinogenicity

The only molybdenum compound that has been shown to produce tumors in animals is the inorganic pigment, Molybdenum Orange, a lead chromate, sulfate, and molybdate compound (Maltoni et al. 1982). In this work, 30 mg of the compound in 1 mL of saline was administered to 20 male and 20 female Sprague-Dawley rats, 13 weeks old. The dose was delivered by subcutaneous injection. After 117 weeks 90% of the animals developed sarcomas at the injection site. None of the controls that received 1 mL of saline developed sarcomas at the injection site. However, since both lead and chromate are contained in this pigment, it is possible that the effect was due to one or both of those metals and not molybdenum.

2. Mutagenicity

An assay developed by Nishioka (1975) was used to test the potential mutagenicity of 56 metal compounds, including both potassium and ammonium molybdate. This assay uses the fact that bacteria normally possess the capacity to repair physical and chemical lesions in their DNA. The normal (wild type) strains are designated Rec^+, for recombination which seems to be crucial in some forms of DNA repair. Recombination-deficient strains are called Rec^-. Nishioka observed that Rec^- cells are usually killed more readily by any DNA-damaging agent than Rec^+ cells. While a positive result does not prove mutagenesis, it is reasonable to suspect mutagenicity for a chemical that is more inhibitory to Rec^- cells than to Rec^+ cells. Both potassium and sodium molybdate gave positive results in this test.

3. Reproductive/Teratogenic Effects

The study by Jeter and Davis (1954) described in Section V.B. showed that oral doses of approximately 8 and 14 mg Mo/kg/day (as sodium molybdate) caused a high rate (75%) of infertility in male rats. Moreover, examination of the testes revealed various degrees of seminiferous tubule degeneration. In the same study, female rats fed a dose of 70 mg Mo/kg/day for ten days showed irregular estrus cycles over a five-week period.

Thomas and Moss (1951) studied the effect of molybdenum on growth, spermatogenesis and testes of young dairy bulls. They used two male Holstein calves, 190 and 217 days old at the beginning of the test. The experimental period was 129 days after which they were slaughtered and tissues taken for examination.

The calves were given sodium molybdate by capsule daily. The dose was calculated to be between 4.1 and 6.8 mg Mo/kg/day for one animal and between 4.8 and 7.8 mg Mo/kg/day for the other animal.

In addition to symptoms such as diarrhea, stiffness, lethargy and hair color changes which have been described elsewhere, the authors note that the most marked symptom was the lack of libido. At no time during the period of molybdenum feeding did the calves exhibit any sign of libido or sex interest, even though they were occasionally allowed to run with cows and stilbestrol-injected heifers.

A histological examination of the testes showed various stages of degeneration in the seminiferous tubules. It appeared that the effect of the molybdenum poisoning, "was a gradual disappearance of the spermatogenetic and interstitial tissue, the spermatogenic tissue possibly being first attacked and a wave of disintegration progressing from the center of the tubule outward."

As described in Section V.C., Schroeder and Mitchener (1971) observed that when Charles River CD strain mice were administered drinking water containing 10 mg Mo/L as the molybdate ion from time of weaning and allowed to mate, there was an increased number of early deaths in their offspring. Moreover, the surviving offspring, which were also administered the same drinking water, had increased numbers of maternal deaths, dead litters and runts in the F_3 generation.

Suttle and Field (1969) have shown that female sheep fed a diet low in copper (1 mg/kg) and high in both molybdenum (25 mg/kg) and sulfate (0.53%) tended to develop reproductive failure. Thirty-three Scottish Blackface ewes, 3.5 to 5.5 years old and weighing 50 to 55 kg were placed on four different diets: (1) a basal diet low in copper (Group A); (2) the basal diet with a copper supplement (10 mg/kg, form not reported, Group B); (3) the basal diet with 25 mg Mo/kg and 0.53% sulfate (salts not reported, Group C); (4) the basal diet with added copper (10 mg/kg), molybdenum (25 mg/kg), and sulfate (0.53%) (Group D). (These diets are the same as those in Suttle and Field 1968a,b). The ewes were bred and kept on a food consumption of 1.25 kg up to the beginning of the last month of pregnancy, 1.5 kg for the remainder of pregnancy, and 2.0 kg during lactation. The surviving ewes and lambs were slaughtered 10 to 11 weeks after parturition. The number of ewes in each group were 8, 6, 14 and 5 for groups A, B, C and D, respectively.

Most of the ewes from groups A, B, and D held to first service and all produced lambs. In group C only six of the ewes conceived. The lambing percentages (number of lambs born divided by number of ewes in group) were 150 (group A), 133 (group B), 180 (group D) and 100 (group C).

All the lambs from groups B and D (copper-supplemented groups) were healthy at birth and were in good condition until slaughter. Three of the lambs from group C died shortly before birth and three, born in a very weak condition, were unable to rise and were slaughtered. All of the stillborn lambs in group C and those showing incoordination at birth had severe lesions of the brain and spinal cord typical of swayback. These included cavitation of the cerebral white matter and chromatolysis of the red and vestibular nuclei. One lamb also showed cerebellar hypoplasia. The only apparently healthy lamb in group C showed lesions characteristic of swayback when slaughtered at ten weeks of age.

Of the nine lambs in group A, one showed characteristic symptoms of swayback at eight weeks and another slight signs of incoordination at ten weeks but the remainder showed no clinical abnormalities.

Thus, both decreased fertility and the production of congenital swayback in lambs were observed in ewes that received a low copper (1 mg/kg) diet with 250 mg Mo/kg + 0.53% sulfate added. Assuming a weight of 60 kg for the ewes and a consumption of 2400 g/day of food, 25 mg Mo/kg in the diet would correspond to 1 mg Mo/kg/day.

E. Beneficial Effects

Molybdenum is generally considered to be an essential element because of the role it plays as a cofactor in the metallo-enzymes xanthine oxidase, aldehyde oxidase and sulfite oxidase (Cohen et al. 1974, Underwood 1971, Davies 1977). These enzymes are involved in the metabolism of hypoxanthine and xanthine to form uric acid, the oxidation of alcohol to acetic acid and the oxidative metabolism of the sulfur moiety of sulfur-containing amino acids. Sulfite oxidase is also important in metabolizing exogenous bisulfite and SO_2 (Cohen et al. 1973).

It is difficult to create a diet so low in molybdenum that it is deficient. Experimental deficiencies have been created in rats (Johnson and Rajagopalan 1976) by administering tungsten which acts as a molybdenum antagonist and leads to loss of sulfite oxidase and xanthine oxidase in the livers of the treated animals. Thus, the requirement for molybdenum is very low.

Luo et al. (1983) have recently shown that the addition of either 2 or 20 mg Mo/L (as sodium molybdate) to the drinking water of rats dosed with N-nitrososarcosine ethyl ester (NSEE) significantly inhibited NSEE-induced esophageal and forestomach carcinogenesis. The rats used were Sprague-Dawley male weanlings weighing about 55 g. The experiment lasted 30 weeks. Assuming a young rat weighing 0.1 kg consumes 10 g of water per day, then 2 and 20 mg Mo/L in the water would be equivalent to 0.2 and 2 mg Mo/kg/day.

Yamane and Koizumi (1982) reported a protective effect of molybdenum on the toxicity of mercuric chloride. Thirty-five male Wister strain rats weighing an average of 170 g (age not given) were divided into four groups. There were five animals in group 1 and 10 each in groups 2, 3 and 4. Group 1 consisted of controls. Group 2 rats received 120 mg Mo/kg day as sodium molybdate dissolved in saline by ip injection for three days. Group 3 rats were given a single ip injection of mercuric chloride dissolved in saline at a dose of 0.03 mmol/kg. Group 4 rats received the same injections of molybdenum mercuric chloride as group 2, followed 24 hours later by the same mercuric chloride injection as group 3. The animals were observed for six days after the mercuric chloride treatment.

After two days all the animals in group 3 died. None of the other groups had fatalities through the observation period of six days. Tissue studies revealed that the mercury content of the livers, kidneys and spleens of rats in group 4 had significantly ($P<0.05$) less mercury than those in group 3. The authors suggested that molybdenum might influence absorption and/or excretion of mercury.

F. Summary

There is considerable variability in the acute toxicity of molybdenum, depending on both the chemical compound and the animal species. Generally, the more soluble the compound the more toxic it is. For compounds such as molybdenum trioxide, ammonium molybdate and sodium molybdate (which contain molybdenum in the hexavalent state), the lethal dose by the oral route for laboratory animals such as rats, guinea pigs and rabbits is on the order of 100 to 300 mg/kg/day. Histological examinations of animals following acute doses generally show damage to the liver, kidney and sometimes the adrenals and spleen. Cattle and sheep are more sensitive to molybdenum poisoning than other animals. Due to the expense of these animals, good statistical data on acute toxicity is sparse. However, several experiments show a severe toxic effect at levels of 4 to 7 mg/kg/day or lower that would probably be fatal if allowed to proceed.

Molybdenum acts as a biological antagonist to copper. As a result, the reaction of an animal to increased molybdenum intake can, and often does, depend on the dietary copper history of the animal. An animal that is copper-deficient is generally much more susceptible to molybdenum toxicity than one on an adequate dietary copper intake, and addition of copper can often reverse the symptoms of molybdenum toxicity. Moreover, sulfur plays an important and complicated role. Generally, sulfate provides protection against molybdenum toxicity in monogastric animals (except when they are copper deficient--in which case it can intensify the toxic symptoms). However, in ruminants sulfate tends to greatly increase the toxicity of molybdenum. Since it is impossible to account for the copper and sulfate status of the general population, this copper-molybdenum-sulfur interaction will not be belabored here.

The addition of molybdenum to diets of animals at less than lethal levels can give rise to a number of responses. In rats this ranges from a decreased growth rate which occurs at intakes of 2 to 8 mg Mo/kg/day and higher, while higher doses (8 to 14 mg Mo/kg/day) produce achromotrichia (depigmentation of the hair), alopecia, male infertility and testicular degeneration. At doses of 50 mg/kg/day, diarrhea and weight loss are often reported. Changes in copper status, such as a loss of copper stored in the liver, leading to an induced copper deficiency are often reported. An effect which seems to be shared by a number of species involves bone or joint abnormalities. This effect has been observed in rats at molybdenum intake levels ranging from 7.5 to 50 mg/kg/day.

Guinea pigs seem to be somewhat less sensitive to molybdenum toxicity. They show decreased weight gains at about 40 mg/kg/day and weight losses above 160 mg Mo/kg/day. They also are susceptible to achromotrichia (at 80 mg Mo/kg/day). At intakes greater than 40 mg Mo/kg/day, the livers of guinea pigs lose some of their copper stores. However, very subtle effects of molybdenum on dietary copper have been shown by first depleting guinea pigs of some of their copper stores and then repleting these stores. The addition of molybdenum (at doses as low as 0.3 mg Mo/kg/day) at the time of copper repletion has adverse effects on the rate of repletion.

Rabbits tend to develop many of the symptoms displayed by rats. They develop numerous toxic symptoms at an intake of about 30 mg Mo/kg/day, including anorexia, weight loss, alopecia, dermatosis, anemia and a foreleg deformity. An intake of 66 mg Mo/kg/day has been shown to affect the appetite and cause thyroid dysfunction. An increase in serum sulfhydryl groups was observed in rabbits receiving 0.5 mg Mo/kg/day and higher.

No effect on the growth of pigs receiving 2 mg Mo/kg/day as sodium molybdate was observed over a four-month period. However, these animals did show a lower liver copper content than controls.

Cattle develop severe diarrhea at molybdenum intakes (generally as sodium molybdate) of 4 to 7 mg Mo/kg/day. Other symptoms include emaciation, achromotricia, lethargy, cessation of milk synthesis, a foreleg abnormality and infertility. As mentioned earlier, cattle and sheep react quite differently from monogastric animals in that the addition of sulfate to the diet exacerbates the molybdenum toxicity.

Exposure of mice to 10 mg Mo/L in drinking water (about 1.5 mg Mo/kg/day) over several generations led to increased early deaths of offspring, increased numbers of dead litters and maternal deaths and increased numbers of runts.

One mutagenicity test indicated the possibility that sodium molybdate and potassium molybdate might be mutagenic.

In addition to the reproductive effects noted in rats and cows where both male infertility and seminiferous tubule degeneration are observed following elevated molybdenum levels, there are studies showing that molybdenum causes infertility in female sheep. When administered in conjunction with sulfate to ewes on a low copper diet, molybdenum exposure can lead to congenital swayback in the offspring.

Although it is difficult to construct a diet so low in endogenous molybdenum that a deficiency can be induced, the presence of molybdenum in metallo-enzymes such as sulfite oxidase and xanthine oxidase implies that molybdenum is a required micronutrient for mammals. There is recent evidence that molybdenum offers protective effects against some kinds of esophageal cancers and mercury toxicity.

VI. HEALTH EFFECTS IN HUMANS

A. Clinical Case Studies

Molybdenum is considered essential for health, but reported cases of molybdenum deficiency are rare. However, deficiencies in enzymes containing molybdenum have been reported in humans. In one case reported by van der Heiden et al. (1979), a three-week-old child was observed to have deficiencies in both xanthine and sulfite oxidase. This patient exhibited a very low uric acid level and significantly increased urinary xanthine and hypoxanthine. This same child was studied at three years of age by Johnson et al. (1980) who diagnosed a combined deficiency of sulfite oxidase and xanthine dehydrogenase. This patient also exhibited an abnormal distribution of urinary metabolites (including sulfite, s-sulfocysteine, taurine, xanthine, hypoxanthine and uric acid). Hepatic sulfite oxidase and xanthine dehydrogenase activity levels were measured at below the limits of detection. The patient exhibited neurological disorders, dislocated ocular lenses and failure to thrive. However, the patient had normal levels of blood serum molybdenum, ruling out a dietary deficiency. The authors postulated that a metabolic disorder, possibly genetic, was responsible for a defect in the incorporation of molybdenum into the enzymes. Additional cases of similar disorders have been reported (Johnson et al. 1980).

Until recently there have been no reports of frank molybdenum deficiencies in laboratory animals or humans. Abumrad et al. (1981) reported that a 24-year-old man developed an amino acid intolerance during prolonged total parenteral nutrition that was reversed by molbydate therapy. This patient was suffering from Crohn's disease (duration of 12 years). He underwent multiple small bowel resections with a resultant small bowel syndrome requiring maintenance on total parenteral nutrition (TPM) in the last 18 months of his life.

During the last six months of TPN administration the patient developed tachycardia, tachypnea, severe headache, night blindness, nausea, vomiting and central scotomas. These symptoms progressed in 24 to 48 hours to severe generalized edema, lethargy, disorientation and coma and were associated with high plasma methionine and low serum uric acid. After attempting a lowering of sulfur-containing amino acids in the TPN solution and infusions of sodium bisulfate without success, the patient was given an ammonium molybdate supplementation of 0.3 mg/day with a lower daily intake (12.3 mmol/day compared to 23.7 mmol/day) of sulfur amino acids. This treatment produced a progressive reversal of all biochemical abnormalities. The authors attributed the initial problem to a diet-induced combined deficiency of two molybdo-enzymes, sulfite oxidase (leading to the high plasma methionine) and xanthine oxidase (leading to the low serum uric acid). This may be the first reported case of a diet-induced molybdenum deficiency in humans.

Deosthale and Gopalan (1974) studied the effects of dietary molybdenum levels on uric acid and copper excretion in humans. Four subjects were fed diets which provided molybdenum intakes of 160, 540 and 1,540 μg Mo/day (corresponding to 0.002, 0.008 and 0.022 mg Mo/kg/day, respectively). Urinary excretion of uric acid was not affected by molybdenum intake. However, serum copper levels were elevated and copper excretion in the urine was increased from 24 μg/day (low molybdenum diet) to 77 μg/day by the high molybdenum diet. Fecal copper levels were unaffected. This indicated that dietary molybdenum had no effect on copper absorption, but favored mobilization of tissue copper. The mean copper excretion with the low molybdenum diet was 24 μg/day. This value increased to 77 μg/day with the high molybdenum diet.

B. Epidemiological Studies

Krishnamachari and Krishnaswamy (1974), investigated the cause of a particular bone deformity, Genu valgum, in a high fluoride area of India. High fluoride intake was not associated with this particular syndrome, but nutritional and dietary surveys of this population revealed a high molybdenum content in the cereals which were locally grown and consumed. Since animal studies have shown that molybdenum increases urinary copper excretion and copper depletion from the body interferes with bone formation, it was suggested that this form of osteoporosis was a consequence of the high molybdenum content of the diet.

In an attempt to determine the cause of a gout-like illness in a molybdenum-rich province in Russia, Koval'skiy et al. (1961) measured molybdenum levels in blood and urine, as well as xanthine oxidase activity in blood and uric acid content in the blood and urine. The exposed population had an estimated daily dietary intake of 10 to 15 mg Mo (0.14 to 0.21 mg Mo/kg/day) and 5 to 10 mg Cu. The study population consisted of 300 persons (184 adults) who lived in an older settlement in the molybdenum-rich area, and 100 persons (78 adults) from a newer adjacent settlement. Gout symptoms were characterized by pains in the joints, especially the knee and metatarsophalangeal joints of the legs and the phalangeal joints of the hands. These symptoms were detected in 57 (31%) adults in the older settlement and 14 (18%) adults in the newer settlement. According to the authors, normal frequencies of these symptoms are no more than 1% to 4%. In all cases, the illness was accompanied by an increase in uric acid content of the blood. Enlargement of the liver and gastrointestinal tract, liver and kidney illnesses were observed. Detailed examinations of 52 persons from the molybdenum-rich area and five persons from a control area outside the molybdenum-rich province were performed. For the control population, estimates of daily intake were 1 to 2 mg Mo (0.014 to 0.028 mg Mo/kg/day) and 10 to 15 mg Cu. Increased blood levels of molybdenum, xanthine oxidase and uric acid were observed in the study population. Copper levels were decreased in blood and increased in urine. The authors proposed that the high molybdenum intake was causally related to the development of the gout-like illness. The relatively high dietary intakes of both molybdenum and copper in the control group complicate the interpretation of the data.

This study, however, does have some weaknesses. First, even the control population has a fairly high intake of molybdenum and copper (NAS 1980a). Secondly, the ability of molybdenum to induce or activate xanthine oxidase has not been conclusively demonstrated in an animal model. Indeed, Cox et al. (1960)

found a reduction of liver xanthine oxidase activity in rats given excess dietary molybdenum. Thus, the connection between excess molybdenum intake and gout is in doubt.

Walravens et al. (1979) studied 25 workers at a roasting plant in Denver, Colorado where MoS_2 is converted to MoO_3. An eight-hour time-weighted average concentration of 1.02 mg Mo/m^3 (respirable dust) was utilized to determine a minimum daily body burden of molybdenum at this plant of 10.2 mg Mo (0.15 mg Mo/kg/day). Twenty-four controls were obtained from students and medical center personnel. In response to a medical questionnaire, workers' complaints were nonspecific. Of the controls, 14 of the 24 had plasma molybdenum concentrations less than 5 μg Mo/L (lower limit of detection). Only ten workers had blood molybdenum concentrations within the range of the control values. The remaining 15 workers had blood molybdenum levels which ranged from 35 to over 300 μg Mo/L. Increases in serum ceruloplasmin were proportional to increases in serum copper levels. Mean serum ceruloplasmin level of the 25 workers was 50.47 ± 1.38 mg/100 mL which was significantly higher than the control mean of 30.50 ± 1.33 mg/100 mL ($P<0.005$).

Serum uric acid levels were significantly different from the controls ($P<0.025$). The authors cautioned against the use of ceruloplasmin and uric acid levels as indicators of molybdenum exposure due to the many confounding influences upon these measures. More reliability was placed upon the plasma and urine molybdenum values as indicators of exposure.

Twenty-four hour urine samples were collected from only 14 workers. None were obtained from the controls. Of the samples collected, urinary molybdenum levels were elevated in 12. However, with only one exception, urinary copper levels were within normal values (Table VI-1).

Chappell et al. (1979) compared individuals from two cities in Colorado with low and high levels of molybdenum in the water. Denver was used as the control city where water molybdenum concentrations ranged from 1 to 50 μg Mo/L. Blood samples from 42 males ranged from below the detection limit (5 μg Mo/L) to as high as 34 μg Mo/L. Mean ceruloplasmin levels in serum equaled 30.41 ± 1.03 mg/dL and the mean the serum uric acid level was 5.34 ± 0.20 mg/dL. Urinary molybdenum content was 87 ± 18 μg and urinary copper content was 12.7 ± 1.5 μg Cu over a 24-hour period.

Golden, Colorado, with water molybdenum concentrations equal to or greater than 200 μg Mo/L, was considered the exposed area. The exposed population consisted of 13 college students from the city of Golden. Assuming consumption of 2 liters per day, the exposure was 400 μg Mo/day or 0.006 mg Mo/kg/day for a 70-kg person. Daily urinary excretion of molybdenum was higher in the exposed population as compared to the controls (186 ± 34 μg versus 87 ± 18 μg, respectively). Excretion of copper in the urine did not differ between the two groups. Higher values for serum ceruloplasmin (40.31 ± 2.85 mg/dL versus 30.41 ± 1.03 mg/dL) and lower values of serum uric acid (4.35 ± 0.46 mg/dL versus 5.34 ± 0.20 mg/dL) were found to be significant within the exposed group when compared to the controls.

Table VI-1 Plasma Mo, Urinary Mo and Urinary Cu Levels of 14 Exposed Workers: Mean, range and normal range.

Workers (N=14)	Plasma Mo ng/mL	Urinary Mo µg/L	Urinary Cu µg/L
Mean	120.64	1,790.00	33.14
Range	9-364[a]	120-11,000[b]	5-347[c]
Normal range	0-34	20-230	40

[a] 5 workers with values <100 ng/mL.
[b] 7 workers with values <1,000 µg/L.
[c] 1 worker with value <40 µg/L.

Adapted from Walravens et al. (1979).

Changes in the water molybdenum concentration in Golden over time (1975 to 1977) from 200 μg Mo/L to 49 μg Mo/L yielded a normalization of the serum ceruloplasmin levels and a decrease in mean daily urine molybdenum excretion. By 1977 the serum uric acid and plasma molybdenum levels were within the normal range.

Further studies by Chappell et al. (1979) on serum ceruloplasmin, serum uric acid and urinary molybdenum and copper levels in inhabitants of cities with various (20 to 200 μg/L) molybdenum levels within the water supplies yielded no differences in those parameters. The authors found it encouraging that the plasma molybdenum levels were within the normal range (5 to 34 μg Mo/L) among subjects who were consuming water with up to 200 μg Mo/L. Increased ingestion of molybdenum led to an increase in urinary excretion of the element.

Briese (1976) performed a geographic study of mortality in Colorado to determine if mortality and/or morbidity (cancer incidence) was related to specific areas within the state. Although a geographic difference was found, the differences were not statistically significant and the influence of molybdenum on mortality and/or morbidity was unobtainable from these data.

Table VI-2 summarizes the health effects of increased molybdenum intake in humans.

Table VI-2 Summary of Health Effects of Increased Molybdenum Intake in Humans

Reference	Intake mg/kg/day	Observed effects
Deosthale and Gopalan (1974)	0.022 (diet)	Increased plasma Cu, increased urinary Cu, no effect on urinary uric acid
Krishnamachari and Krishnaswamy (1974)	Increased Mo in Grain	Bone deformity
Koval'skiy et al. (1961)	0.14-0.21 (diet)	Gout-like symptoms, increased Mo, uric acid, xanthine oxidase in blood and urine, increased Cu in urine, decreased Cu in blood
Walravens et al. (1979)	0.15 (Lung)	Increased blood and urine Mo, increased blood Cu and ceruloplasmin, normal urinary Cu, no specific adverse effects
Chappell et al. (1979)	>0.006 (drinking water)	Increased urinary Mo, no change in urinary Cu, decreased serum uric acid, increased serum ceruloplasmin
	0.0005-0.006 (drinking water)	Normal serum Mo

Lack of dietary molybdenum may have adverse health effects. In China, the epidemiology of esophageal cancer was studied with respect to geographical distribution, risk factors and preventive measures (Li 1982). Examination of high-risk areas, as defined by excess mortality, revealed deficiencies of molybdenum, copper, cobalt, zinc, manganese and iron in the drinking water, and deficiencies of molybdenum, nickel, manganese, tin and iron in food. Serum, hair and urine levels of molybdenum, zinc and magnesium were low in the high risk areas. In Africa, food plants grown on molybdenum-deficient soils are a possible source of nitrosamines and have been linked to the high incidence of esophageal and stomach cancers of this country (Langman 1971). An earlier study by the Cancer Institute of the Chinese Academy of Medical Services, cited by Li (1982), found that ammonium molybdate significantly reduced the incidence of gastric adenocarcinomas in animals exposed to N-nitroso compounds.

C. High Risk Subpopulations

Dietary intake and balance studies described in Section III.D. indicated that children are exposed to more molybdenum per body weight than adults. Whether this constitutes a high-risk population is unknown at this time. In addition, those persons who are copper deficient may be considered at high risk to the effects of molybdenum, particularly if they have a high sulfate coutent in their diet.

D. Summary

Little information is available regarding the health effects of molybdenum in humans. Molybdenum is considered to be required for health and is a component of several important metabolic enzymes (e.g., sulfite oxidase and xanthine oxidase). Because molybdenum is present in most food and water, cases of molybdenum deficiency are rare. In areas where molybdenum is low in food or water, there is a suggestion of an increased rate of gastrointestinal cancers.

Oral ingestion of excess molybdenum may have adverse health effects. A particular bone disease in India may be a consequence of ingestion of molybdenum-rich grain, resulting in depletion of normal tissue levels of copper. In a clinical study, ingestion of 0.16 to 1.54 mg Mo/day resulted in increased urinary excretion of copper.

In a molybdenum-rich area of Russia, where average daily intake of molybdenum is 10 to 15 mg/day there was a reported increase in xanthine oxidase and uric acid content in blood and urine and a high incidence of a gout-like disease. However, workers at a molybdenum roasting plant exposed to an average daily dose of about 10 mg (from inhaled dust), did not display any specific adverse effects attributable to molybdenum.

Comparisons of blood and urine samples from individuals living in Denver (averages water concentration from 1 to 50 μg Mo/L) and Golden, Colorado (average water concentration above 200 μg Mo/L) revealed increased urinary excretion of molybdenum, increased serum ceruloplasmin and decreased serum uric acid levels in individuals from Golden. No adverse health effects were noted. When the molybdenum content of water in Golden was decreased, the blood and urine levels of molybdenum, uric acid, and ceruloplasmin returned to normal. No significant differences in blood or tissue levels of molybdenum were observed among various other cities with water molybdenum concentrations ranging from 20 to 200 µg Mo/L.

While no experiments identify any group as a high-risk subpopulation, children typically ingest and absorb more molybdenum per unit body weight than adults, and so might be at an increased risk. Likewise, since molybdenum ingestion is associated with depletion of body copper stores, individuals who are copper deficient may also be at an increased risk.

VII. MECHANISM OF TOXICITY

A. Xanthine Oxidase and Gout

One of the few studies linking molybdenum to a specific disease in humans is the work by Koval'skiy et al. (1961). This epidemiological study discussed in Section VI showed a link between increased dietary molybdenum intake and the incidence of gout. The researchers reported an increase of xanthine oxidase activity and uric acid content in the blood and urine. The authors suggested that since xanthine oxidase contains molybdenum, the increased molybdenum in the diet would lead to an increased synthesis of this enzyme, which would catalyze increased conversion of xanthine to uric acid, leading to the gout-type disease. The authors noted that while a noticeable increase of uric acid has not been observed in laboratory animals receiving molybdenum, this could be explained by the presence of active uricase in animals. As mentioned in the last Section, the activation or induction of xanthine oxidase by molybdenum has also not been shown in animals. Thus, the connection between gout and molybdenum has not been clearly demonstrated.

B. Weight Gain Reduction

Elevated intake of molybdenum causes retardation of growth, and at higher levels, loss of weight in experimental animals. This is generally accompanied by anorexia. One possible mechanism that has been proposed is that the animals voluntarily reject the high molybdenum diet because of taste or some association with a gastrointestinal disturbance (Underwood 1971). Monty and Click

(1961) described an experiment that indicated that rats could learn to discriminate between a diet containing toxic (800 mg Mo/kg as sodium molybdate) and non-toxic levels of molybdenum. These authors proposed that an interaction of molybdate with other dietary constituents was involved in this response. However, Johnson and Miller (1963) found evidence that the growth depression of rats on high molybdenum diets is not simply due to decreased consumption. They observed a decreased utilization of nutrients in the diet and suggested that dietary molybdenum inhibits some facet of protein synthesis.

C. Synergistic/Antagonistic Effects

The antagonism between molybdenum and copper has presented a tremendous challenge to researchers who have attempted to study this interaction. This interaction is further complicated by the interaction of molybdenum with dietary sulfur. A considerable body of research has been performed on the molybdenum-copper-sulfur interaction and, while interesting, its relevance to the issue of molybdenum toxicity in humans is not entirely clear. Thus, only a cursory discussion will be given here.

As mentioned earlier (Section III), ruminants and monogastric animals differ markedly in their reactions to added molybdenum and sulfate in the diet. In ruminants, very low molybdenum concentrations (10 mg Mo/kg in the diet) result in tissue copper depletion (Suttle 1980) which is potentiated by dietary sulfate. In nonruminants, the effect of molybdenum on copper is alleviated by the addition of sulfate to the diet. The effect occurs at higher concentrations (>100 ppm Mo) in the diet and generally results in tissue copper accretion.

The mechanism for the molybdenum-copper-sulfur interaction remains unexplained, although there have been models proposed. Dowdy and Matrone (1968) demonstrated that a copper-molybdenum complex can exist in vivo and that the copper bound in the complex is biologically unavailable. Their model (Dowdy et al. 1969) involves the formation of this complex which resembles a rare natural mineral, lindgrenite ($2CuMoO_4 \cdot Cu(OH)_2$), in vivo, thereby giving a mechanism for the biological antagonism between copper and molybdenum. This hypothesis does not, however, completely explain the interaction with sulfur and the differences between ruminents and nonruminents. Suttle (1980) suggested that thiomolybdates such as MoS_4^{2-} play an intermediate role. This model, which remains to be substantiated, involves the interaction of S^{2-} and molybdate in the rumen to form thiomolybdates which subsequently interact with copper. This interaction in ruminents presumably leads to the formation of a biologically unavailable compound ($CuMoS_4$). However, nonruminents have a limited capacity for S^{2-} production in the gut. Suttle has speculated that thiomolybdates might be formed systemically as a consequence of the inhibition of sulfite oxidation by molybdate. He suggests that this leads to tissue accretion of copper as it becomes tied up with the thiomolybdates. He then suggests that sulfate alleviates the copper-molybdenum antagonism by blocking the absorption of molybdenum and decreasing thiomolybdate formation.

Mills et al. (1981) observed the effects of feeding rats diets containing molybdate, sulfide and thiomolybdates. The thiomolybdate diets produced responses similar to those seen in ruminants. Moreover, when molybdate was given in conjunction with S^{2-}, the molybdate effect was increased. This would indicate that if there are human diets that contain unusual amounts of S^{2-} (comparable to the molybdate intake), these people could be at higher than normal risk.

VIII. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

The quantification of toxicological effects of a chemical consists of an assessment of the non-carcinogenic and carcinogenic effects. In the quantification of non-carcinogenic effects, an Acceptable Daily Intake (ADI) is calculated. From this an Adjusted Acceptable Daily Intake (AADI) and Health Advisory (HA) values for the chemical are then calculated to define the appropriate drinking water concentrations to limit human exposure. For ingestion data, this approach is illustrated as follows:

$$\text{ADI} = \frac{(\text{NOAEL or LOAEL in mg/kg/day})(\text{Body Weight in kg})}{\text{Uncertainty/Safety Factor}} = \text{mg/day}$$

$$\text{AADI} = \frac{\text{ADI}}{\text{Drinking Water Volume in L/day}} = \text{mg/L}$$

where:

NOAEL = no-observed-adverse-effect level.

LOAEL = lowest-observed-adverse-effect level.

Body weight = 70 kg for adult or 10 kg for child.

Drinking water volume = 2 L per day for adults or 1 L per day for children.

Uncertainty/Safety Factor = 10, 100 or 1,000.

Utilizing these equations, the following drinking water concentrations are developed for non-carcinogenic effects:

1. A one-day HA for 10-kg child.
2. A one-day HA for 70-kg adult.
3. A ten-day HA for 10-kg child.
4. A ten-day HA for 70-kg adult.
5. A lifetime AADI for a 70-kg adult.

The distinctions made between the HA calculations (items 1 through 4) are associated with the duration of anticipated exposure. Items 1 and 2 assume a single acute exposure to the chemical. Items 3 and 4 assume a limited period of exposure (possibly 1 to 2 weeks). The HA values will not be used in establishing a drinking water standard for the chemical. Rather, they will be used as informal scientific guidance to municipalities and other organizations when emergency spills or contamination situations occur. The AADI value (item 5) is intended to provide the scientific basis for establishing a drinking water standard based upon non-carcinogenic effects.

A NOAEL or LOAEL is determined from animal toxicity data or human effects data. For animal data, this level is divided by an uncertainty factor because there is no universally acceptable quantitative method to extrapolate from animals to humans. The possibility must be considered that humans are more sensitive to the toxic effects of chemicals than are animals. For human data, an uncertainty factor is also used to account for the heterogeneity of the human population in which persons exhibit differing sensitivity to toxic chemicals. An Office of Drinking Water (ODW) modification of the guidelines set forth by the National Academy of Sciences (NAS 1977, 1980) is typically used in establishing uncertainty factors as follows:

- An uncertainty factor of 10 is used when good acute or chronic human exposure data identifying a NOEL/NOAEL are available and are supported by acute or chronic toxicity data in other species.

- An uncertainty factor of 100 is used either when good acute or chronic toxicity data identifying NOEL/NOAEL are available for one or more animal species (but human data are not available), or when good acute or chronic toxicity data identifying a LOAEL in humans are available.

- An uncertainty factor of 1,000 is used either when limited or incomplete acute or chronic toxicity data are available, or when good acute or chronic toxicity data identify a LOAEL (but not a NOEL/NOAEL) for one or more animal species.

The uncertainty factor used for a specific risk assessment is judgmental. Factors that cannot be incorporated in the NAS/ODW guidelines for selection of an uncertainty factor, but must be considered include: (1) the quality of the toxicology data, (2) the significance of the adverse effect and (3) the existence of counterbalancing beneficial effects.

If toxicological evidence requires the chemical to be classified as a potential carcinogen (there is insufficient evidence to classify molybdenum as a carcinogen following ingestion), mathematical models are used to calculate the estimated excess cancer risks associated with the ingestion of the chemical via drinking water.. The bioassay data used in these estimates are from animal experiments. In order to predict the risk for humans from these data, it must be converted to an equivalent human dose. This conversion includes correction for non-continuous animal feeding, non-lifetime studies and for the difference in size. The factor that compensates for the size difference is the cube root of the ratio of the animal and human body weights. It is assumed that the average human body weight is 70 kg and that the average human consumes 2 liters of water per day. The multistage model is then fit to the equivalent human data to estimate the risk at low doses. The upper 95% confidence limit of this estimate is used. Excess cancer risks can also be estimated using other models such as the one-hit model, the Weibull model, the logit model and the probit model. There is no basis in the current understanding of the biological mechanisms involved in cancer to choose among these models. The estimates of low doses for these models can differ by several orders of magnitude.

The scientific data base used to calculate and support the setting of risk rate levels has an inherent uncertainty. This is because the tools of scientific measurement, by their very nature, involve both systematic and random error. In most cases, only studies using experimental animals have been performed. There is thus uncertainty when the data are extrapolated to humans. When developing risk rate levels, several other areas of uncertainty exist, such as (1) incomplete knowledge concerning the health effects of contaminants in drinking water, (2) the impact of test animal age, sex and species and the nature of target organ systems examined on the toxicity study results and (3) the actual rate of exposure of internal targets in test animals or humans. Dose-response data are usually only available for high levels of exposure, not for the lower levels of exposure for which a standard is being set. When there is exposure to more than one contaminant, additional uncertainty results from a lack of information about possible synergistic or antagonistic effects.

A. Non-Carcinogenic Effects

1. Short-Term Exposure

Fairhall et al. (1945) injected (ip) guinea pigs with molybdenite, molybdenum trioxide, ammonium molybdate and calcium molybdate and observed the animals for 12 months. The strain, sex and age of the animals were not reported. The animals were injected with 2 mL of a solution or suspension of the compounds in isotonic sodium chloride solution. Additional experimental details and the results of this study are provided in Table VIII-1. A dose of 200 mg Mo (800 mg/kg) as ammonium molybdate caused a slowing of respiration. Some animals became cyanotic and all went into convulsions. The authors noted that the salt was strongly acidic. However, a second group of animals receiving 20 mg Mo (80 mg/kg) as ammonium molybdate showed no apparent effects. The majority of the deaths from MoO_3 occurred within two hours. X-Ray photographs of some of the guinea pigs one week after injection showed both calcium molybdate and molybdenite as sharply defined masses in the peritoneal cavity. No similar masses were observed in the guinea pigs surviving MoO_3 injection. The authors noted that both calcium molybdate and molybdenite are insoluble.

Table VIII-1 Mortalities Resulting from the Intraperitoneal Injection of Molybdenum Compounds (Guinea Pigs)

Molybdenum compounds	Amount injected		No. of animals	Mortality (%)			Time on test of surviving animals (months)
	mg of Mo	mg Mo/ kg		4 days	4 weeks	4 months	
Molybdenite	200	800	12	17	17	25	12
Molybdenum trioxide	100	400	8	75	75	75	12
Ammonium molybdate	20	80	8	0	0	0	12
Ammonium molybdate	200	800	12	100	--	--	--
Calcium molybdate	100	400	6	0	0	17	12

Adapted from Fairhall et al. (1945).

Fairhall et al. (1945) performed a similar experiment in which rats received molybdenum compounds in their diet. Molybdenite, molybdenum trioxide, calcium molybdate and ammonium molybdate were fed to white rats (sex and strain unspecified) in amounts ranging up to 500 mg Mo/day (approximately 6,000 mg/kg/day). Table VIII-2 summarizes the results of this study, although it does not give the percent mortality. The authors reported zero mortality for all doses of molybdenite. A mortality of 50% was reported for the lowest doses of the other compounds and 100% for the highest doses. The control group had a 15% mortality over the study period. The LD_{50} values calculated by the authors are given in Table VIII-3.

Pham-Huu-Chanh (1965) described an experiment in which the toxicity of sodium molybdate was compared with that of sodium chromate, tungstate and metavanadate. This work was performed using adult male rabbits (Oryctolagus cuniculus L. Bourgogne stock). The mean weight was 2.50 ± 0.50 kg. The number of animals was not specified. Animals were either conscious or anesthetized with urethane (1 g/kg, ip). Arterial pressure was recorded from the right carotid artery; respiratory movements were followed by recording the endotracheal pressure. The sodium molybdate was administered in a physiological saline at a concentration of 100 mM/100 mL by slow continual perfusion into the femoral vein at a rate such that death took place in 60 ± 10 minutes. The lethal dose in 60 ± 10 minutes was calculated by the author to be 121 ± 53.7 mg Mo/kg. Since only a lethal dose is reported, this study does not provide an estimate of a NOAEL or LOAEL.

Table VIII-2 Distribution of Mo in Tissues of White Rats After Ingestion of Mo Compounds

Compound	No. of animals used	Estimated daily consumption (mg Mo)	No. of days on test	Estimated total intake of Mo (grams)	Average final weight (grams)		Average final weight (grams)		Average dose mg/kg/day based on initial weights		Average Distribution in tissues (mg Mo/10 g fresh tissue)		
					Died	Killed	Died	Killed	Died	Killed	Liver	Kidney	Bone
Molybdenite	8	10	44	0.4	--	82	--	151	--	122	0.02	0.04	0.06
	8	100	44	4.4	--	79	--	146	--	1,266	0.02	0.06	0.05
	8	500	44	22.0	--	79	--	153	--	6,329	0.01	0.04	0.06
Molybdenum Trioxide	8	10	120	0.9	82	83	91	103	122	120	0.12	0.11	0.23
	10	25	137	1.8	128	183	73	106	195	137	0.08	0.19	0.25
	10	50	137	1.7	140	197	95	140	357	254	0.36	0.33	0.40
	8	100	14	1.1	77	--	58	--	1,299	--	0.24	0.14	--
	8	500	8	3.1	81	--	66	--	6,173	--	0.49	0.39	--
Calcium Molybdate	10	9	137	0.9	143	112	121	140	62.9	80.4	0.04	0.12	0.25
	10	21	128	1.3	122	--	109	--	172	--	0.05	0.21	0.28
	10	43	137	3.2	149	134	102	142	298	320	0.09	0.17	0.34
	10	86	57	3.6	189	--	110	--	455	--	0.08	0.17	0.79
	10	430	17	4.7	175	--	113	--	2,457	--	0.18	0.35	0.37
Ammonium Molybdate	8	10	232	2.3	73	82	102	144	137	122	0.09	0.36	--
	8	100	13	1.0	78	--	58	--	1,282	--	0.16	0.16	0.41
	8	500	9	3.2	85	--	--	60	5,882	--	0.16	0.08	--
Control (Average)	48	0	137	0.0	112	121	140	175	0	0	0.03	0.06	0.05

Adapted from Fairhall et al. (1945).

Table VIII-3 LD_{50} Values for Ingestion of Molybdenum Compounds by White Rats[a]

Compound	LD_{50} mg Mo/kg/day	LD_{50} mg Mo/day
Molybdenum Trioxide	125	10
Calcium Molybdate[b]	101	15
Ammonium Molybdate	333	27

[a] Period of exposure ranged from 8 to 232 days.

[b] Rats receiving calcium molybdate weighed nearly twice as much as rats receiving other compounds.

Adapted from Fairhall et al. (1945).

Suttle (1974) studied the effect of molybdenum supplements in the diet on the utilization of dietary copper by guinea pigs. The liver copper stores of four groups of six male albino (no further description given) guinea pigs weighing about 500 g were depleted by feeding a copper-deficient diet (2 mg Cu/kg). All animals were then repleted on a diet containing 8 mg Cu/kg and 0.6 mg Mo/kg. Molybdenum, as ammonium molybdate, was added to four of the diets to provide 0.6, 4.1, 26.0 and 104 mg/kg of additional molybdenum. The author estimated a daily food consumption of 35 g. Thus, for a 500 g animal, the four dietary molybdenum intakes would correspond to 0.04, 0.3, 1.8 and 7.3 mg Mo/kg/day, respectively, above the controls (i.e., 0.6 mg Mo/kg was included in diets of all control and test animals).

The animals were repleted for 14 days and the increase in liver copper after the repletion period was obtained by comparison with an initial sacrificed group. The authors reported that the initial sacrificed group had a value of 25.3 ± 3.9 ppm Cu (dry weight) in their livers (mean ± standard error). For the 0.04, 0.3, 1.8 and 7.3 mg Mo/kg/day dose groups, the copper-repleted guinea pigs had 85.3 ± 3.8, 71.6 ± 6.6, 57.6 ± 5.9 and 38.3 ± 4.0 ppm Cu in their livers respectively. Total plasma copper increased from 0.468 ± 0.043 mg Cu/L to 3.877 ± 0.221 mg Cu/L from the lowest to highest molybdenum group, respectively. None of this increase was attributable to an increase in ceruloplasmin copper. The authors concluded that molybdenum added to the diet significantly impaired the utilization of dietary copper. This study does show a subtle effect on copper utilization at 0.3 mg Mo/kg/day and could be thought of as providing a LOAEL with 0.04 mg Mo/kg/day representing the NOAEL for this effect. However, it is not clear that this specialized model (copper repletion in a copper-depleted animal) would be useful for estimating health effects in normal animals or humans.

2. Long-Term Exposure

Asmangulyan (1965) studied the effects of molybdenum on the body weight and blood chemistry in rabbits. Twenty rabbits of unspecified age, sex and strain were used and divided into five groups. The control group consisted of five animals. Four rabbits each received oral doses of 50, 5 or 0.5 mg Mo/kg daily, except Sunday, for six months. Three animals received a dose of 0.025 mg Mo/kg/day in a similar manner. The molybdenum was administered as ammonium molybdate.

The author reported that during the six-month experiment no gross symptoms were observed at any dose level. Body weight, hemoglobin content of blood, erythrocyte and leukocyte count in the blood and sulfhydryl (SH) groups in the serum were measured three times before the experiment began and then measured each month during the six-month experimental period. The author also reported that at 5 and 50 mg Mo/kg/day a growth retardation was observed (no data given). A marked increase in serum SH groups (roughly two-fold) was observed in the 50 mg Mo/kg/day group. A somewhat smaller increase was reported in the 5 mg Mo/kg/day dose group and to a lesser extent in the 0.5 mg Mo/kg/day group. No increase in serum SH groups was observed at 0.025 mg Mo/kg/day. Similar increases in SH groups were observed in several organs (particularly the liver and spleen) at the highest doses, but not at the lowest dose (0.025 mg Mo/kg/day). The author also observed decreases in the vitamin C content of the kidney and liver in the highest dose group, but not in the lowest dose group. In addition, the author reported several anomalies in the histological examination of various organs in the highest dose group. The anomalies were present, but to a lesser degree, in the 5-mg Mo/kg/day dose group. This experiment suggests that a dose of 0.025 mg Mo/kg/day may be considered a NOAEL in rabbits. While the molybdenum content of the diet was not reported, it was probably close to that administered to the lowest dose group (a 2-kg rabbit consumes about 60 g of food each day, which means that 1 mg/kg endogenous Mo in the food would equal 0.03 mg Mo/kg/day).

Arrington and Davis (1953) studied the toxicity of molybdenum in 40 Dutch rabbits of both sexes and different ages. Nine rabbits served as controls and 31 were fed sodium molybdate, which was added to their ration at 140, 500, 1,000, 2,000 and 4,000 mg Mo/kg. The basal ration contained 2.7 mg Mo/kg and 16.4 mg Cu/kg. The animals were examined daily for gross symptoms of toxicity. In a parallel experiment, the same diets were fed to 24 weanling rabbits (six weeks old), and body weights were measured weekly.

Rabbits fed 1,000 mg Mo/kg in their diet (30 mg Mo/kg/day, assuming an average weight of 2 kg and a daily food consumption of 60 g) or more developed a toxic syndrome characterized by anorexia, weight loss, alopecia, slight dermatosis, anemia and death. All of the animals, both mature and weanling, on the 4,000-mg Mo/kg diet (120 mg Mo/kg/day) died, with an average survival of 30 days for weanling rabbits and 51 days for mature rabbits. Eighty percent of the weanling and sixty-seven percent of the mature animals on the 2,000-mg Mo/kg (60 mg Mo/kg/day) diet died.

Alopecia was common in affected rabbits (those receiving 30 mg Mo/kg/day or more in their diet), and was accompanied by slight dermatosis with rough, dry, scaly skin. There was a complete loss of hair over various portions of the body. A deformity of the front legs, first noticed as an apparent soreness or weakness, occurred in 7 of the 12 young rabbits that exhibited other signs of toxicity. This progressed until the animals were unable to stand and their legs spread outward. While the ability to move the forelegs was not lost, they could not be maintained in the normal position. In three cases, one or both feet bent inward at the carpus joint. In one rabbit, severe bending and twisting of the humerus was observed. These symptoms were accompanied by a decreased hemoglobin concentration and a decreased number of red blood cells. The first changes in these blood parameters were noticed at the same time as the gross signs of toxicity occurred. Hemoglobin levels and red blood cell counts continued to decrease until the animals died or were given copper therapy.

The growth rate of weanling rabbits was retarded when 1,000 mg Mo/kg (30 mg Mo/kg/day) or more was present in the rations. The lower doses of 140 and 500 mg/kg (4.2 and 15 mg Mo/kg/day) did not alter the growth rate. In addition, none of the other symptoms of molybdenum toxicity were reported at either 4.2 or 15 mg Mo/kg/day. Thus, the NOAEL from this study is 15 mg Mo/kg/day. However, it should be noted that only body weight and gross external signs were monitored. No data were obtained on the effect of molybdenum on tissue copper levels or other subclinical effects which could be important and might appear at molybdenum exposure levels less than those required for gross toxicity.

Winston et al. (1973) studied the effect of cold stress on rats receiving moderately elevated levels of molybdenum in their drinking water. Sprague-Dawley rats of both sexes were used. The animals were 5 to 12 months old; the males weighed between 0.4 and 0.7 kg and the females between 0.22 and 0.35 kg. The animals were divided into four groups of 11 to 12 males (there were 45 males in all) and 2 to 5 females (there were 12 females in all). Two of the groups served as controls (and were maintained at 25°C throughout the experimental period of four days). One control group had received a basal diet containing 1 to 3 mg Mo/kg their entire lives. The other control group had received the same basal diet but was also supplied with drinking water containing an additional 10 mg Mo/kg (as sodium molybdate) for their entire lives. Assuming a water consumption of 20 mL/day, the dose ranges were 0.3 to 0.5 mg Mo/kg/day for the males and 0.6 to 0.9 mg Mo/kg/day for the females. The other two groups had similar diets their entire lives, but were placed in a cold room at 2°C to 3°C for four days. Day length was controlled at 12 hours. Weight changes and food intake were measured daily.

Both the male and female rats which had received 10 mg Mo/kg (0.3 to 0.9 mg Mo/kg/day) in their drinking water for their entire lives lost nearly twice as much weight when placed in the cold room for four days as those that had received no added molybdenum in their drinking water. This difference was highly significant ($P<0.01$). Unfortunately, this study did not involve a number of molybdenum dose levels. Therefore, no dose-response relationship can be established and no useful estimate of a NOAEL or LOAEL can be made.

Schroeder and Mitchener (1971) studied the effects of several trace elements, including molybdenum, in the drinking water of mice. The authors used Charles River CD strain mice that were born in a laboratory specially designed to minimize trace metal contamination. The diet contained 1.95 mg Cu/kg (wet weight) and 0.45 mg Mo/kg (wet weight). Five male-female pairs of animals were randomly selected from litters divided at the time of weaning and were placed in separate cages. The animals were administered 10 mg Mo/kg as molybdate (cation not reported) in their drinking water. The control animals received deionized water. Neither the length of the study nor the water consumption rates for the mice were reported. Assuming that a 20 g mouse would consume 3 g of water per day, 10 mg Mo/L in the water would be equivalent to 1.5 mg Mo/kg/day.

The mice were allowed to breed as often as they could up to six months of age. At weaning, pairs were randomly selected from the first litter (F_1A generation), the second litter (F_1B), and sometimes from the third (F_1C) and allowed to breed to produce F_2A generations. Pairs were likewise selected at random from the first F_2A litters and allowed to breed the F_3A and sometimes the second litter for the F_3B generation. The experiment was terminated with the F_3C generation.

The criteria used to evaluate toxicity were the intervals between litters, the age at which the pair produced their first litter, the ratio of male to female pups, and the numbers of runts, deaths, stillborns, breeding failures and congenital abnormalities. In animals receiving 100 mg Mo/L in the drinking water (approximately 1.5 mg Mo/kg/day), there was an increased number of (1) early deaths of the F_1 offspring ($P<0.001$), (2) early deaths in the F_3 generation offspring ($P<0.0001$), (3) maternal deaths ($P<0.05$) in the F_3 generation, (4) dead litters in the F_3 generation ($P<0.05$) and (5) runts in the F_3 generation ($P<0.0001$) in comparison to the controls. Although the study documents a definitive effect in mice at approximately 1.5 mg Mo/kg/day, it does not define a dose-response relationship because only one dose level of molybdenum was evaluated. Therefore, no conclusion regarding a NOAEL or LOAEL can be drawn from the study.

Chappell et al. (1979) compared the blood and urine of individuals from two cities in Colorado with different molybdenum content in the city drinking water. Denver, where water concentrations ranged from 1 to 50 µg Mo/L, was used as the control city. Golden, with water concentrations equal to or slightly greater than 200 µg Mo/L (which is the value proposed for the NOAEL), was considered the exposed area. Blood samples from 42 Denver males (controls) showed levels of molybdenum from below the detection limit (5 µg Mo/L) to as high as 34 µg Mo/L. Mean ceruloplasmin levels in serum of the controls equaled 30.41 ± 1.03 mg/dL and the mean serum uric acid level was 5.34 ± 0.20 mg/dL, both within the normal range. Average urinary molybdenum excretion was 87 ± 18 µg Mo/day, and urinary copper excretion was 12.7 ± 1.5 µg Cu/day in the Denver subjects.

The exposed population consisted of 13 college students from Golden. Assuming consumption of 2 liters of water per day the average intake was 400 µg Mo/day (0.006 mg Mo/kg/day for a 70-kg adult human). Daily urinary excretion of molybdenum was higher in the exposed population than in the controls (186 ± 34 μg and 87 ± 18 μg, respectively). Excretion of copper in the urine did not differ between the two groups. Significantly higher values for serum ceruloplasmin (40.31 ± 2.55 mg/dL versus 30.41 ± 1.03 mg/dL, $P<0.005$) and lower values of serum uric acid (4.35 ± 0.46 mg/dL versus 5.34 ± 0.20 mg/dL, P value not reported) were observed within the exposed group when compared to the controls.

Changes in the water molybdenum concentration in Golden over time (1975 to 1977) from 200 μg Mo/L to 49 μg Mo/L yielded a normalization of the serum ceruloplasmin levels and a decrease in mean daily urine molybdenum excretion in Golden residents. At the 1977 water molybdenum concentration, the serum uric acid levels were not affected and the plasma molybdenum levels were within the normal range.

Further studies by Chappell et al. (1979) on blood and tissue levels in individuals from cities with various (20 to 200 μg/L) molybdenum levels in the water supplies yielded no evidence of significant differences. The authors found it encouraging that the plasma molybdenum levels were within the normal range (5 to 34 μg Mo/L) among subjects consuming water with up to 200 μg Mo/L. Increased ingestion of molybdenum led to an increase in urinary excretion of the element.

B. Quantification of Non-Carcinogenic Effects

1. One-Day Health Advisory

There is no appropriate oral study in animals or humans to serve as the basis for the one-day Health Advisory (HA). In an effort to provide health guidance from the best available information, the ip study by Fairhall et al. (1945) has been selected to serve as the basis for the 10-kg child one-day HA. The authors noted that a single ip dose of 20 mg Mo (80 mg/kg as ammonium molybdate) did not show any apparent effects in guinea pigs over the following 12 months. These workers also found that the LD_{50} for orally ingested ammonium molybdate was about three times higher than for molybdenum trioxide and calcium molybdate (Table VIII-2). Since molybdate is more likely to occur in water as the calcium or sodium salt than the ammonium salt, it therefore appears prudent to divide the NOAEL for ammonium molybdate (80 mg/kg) by three to account for the potential differential toxicity that may result from exposure to molybdenum trioxide or calcium molybdate. Thus, 27 mg Mo/kg will be chosen as the NOAEL for calculating the one-day HA. No other studies provided a basis for selecting a NOAEL for a single dose.

Since this NOAEL is based on a study using ip as the route of exposure, the absorption of orally ingested molybdate across the gastrointestinal tract must be considered. If absorption following an oral dose is less than 100%, the oral dose required to produce the same effect (or no-effect) as observed in the ip study would be higher. However, several studies discussed in

Section III.A. (e.g., Kosarek 1976) indicate that molybdate ingested in water is almost entirely absorbed (i.e., 100% gastrointestinal absorption is assumed). Thus, assuming 100% absorption, the NOAEL for an oral dose is assumed to be the same as the NOAEL for an ip dose (i.e., 27 mg Mo/kg).

The one-day HA for the 10-kg child is calculated as follows:

One-Day Health Advisory for Child:

$$\frac{(27\ \text{mg/kg/day})\ (10\ \text{kg})}{(1\ \text{L/day})\ (100)} = 2.7\ \text{mg/L}$$

where:

27 mg/kg/day = NOAEL following acute exposure in guinea pigs (Fairhall et al. 1945).

10 kg = assumed weight of child.

1 L/day = assumed water consumption by a 10-kg child.

100 = uncertainty factor. This uncertainty factor was selected based upon the NAS/ODW guidelines in which a NOAEL from an animal study is used.

The ip study by Fairhall et al. (1945) has also been selected to serve as the basis for the 70-kg adult one-day HA.

The one-day HA for the 70-kg adult is calculated as follows using 27 mg Mo/kg/day as the NOAEL (Fairhall et al. 1945):

One-Day Health Advisory for Adult:

$$\frac{(27 \text{ mg/kg/day})\ (70 \text{ kg})}{(2 \text{ L/day})\ (100)} = 9.5 \text{ mg/L}$$

where:

27 mg/kg/day = NOAEL following acute exposure in guinea pigs (Fairhall et al. 1945).

70 kg = assumed weight of adult.

2 L/day = assumed water consumption by a 70-kg adult.

100 = uncertainty factor. This uncertainty factor was selected based upon the NAS/ODW guidelines in which a NOAEL from an animal study is used.

2. Ten-Day Health Advisory

There is no appropriate study from which to derive a ten-day HA. However, the pharmacokinetic studies described in Section III are all consistent in showing a rapid excretion of molybdenum, and there is no basis for assuming that repeated acute exposures would be additive. Thus, a conservative estimate of the 10-day HA is obtained by dividing the one-day HA by 10. This results in ten-day HA values of 0.27 and 0.95 mg/L for children and adults, respectively.

3. Adjusted Acceptable Daily Intake

The study by Chappell (1979) has been selected to serve as the basis for the ADI and AADI. This study observed humans exposed to a range of molybdenum concentrations in drinking water. The results revealed that several biochemical parameters including blood molybdenum levels (an indicator of organ exposure) were within normal ranges when drinking water levels were 0.200 mg/L or less (approximately 0.006 mg/kg/day for a 70-kg adult human).

The ADI for a 70-kg adult is calculated as follows:

ADI:

$$\frac{(0.006 \text{ mg/kg/day})\ (70 \text{ kg})}{(2)} = 0.21 \text{ mg/day}$$

where:

0.006 mg/kg/day = NOAEL following long-term exposure in humans (Chappell 1979).

70 kg = assumed weight of adult.

2 = uncertainty factor. This uncertainty factor was selected because:

a. No adverse health effects were observed in individuals consuming drinking water containing 200 µg Mo/L. In order to be conservative, the minimum safety factor (2) will be applied to account for possible sensitive individuals.

b. Molybdenum is an essential element in animals and humans. An adequate and safe intake for adult humans of 0.15 to 0.50 mg

Mo/day has been established by NAS (1980) and the use of a safety factor of 2 will result in a daily drinking water intake (0.21 mg/day) within this range. Assuming an additional intake of 0.18 mg/day from food, a total daily intake of 0.39 mg/day would still be within the safe and adequate range.

c. These data are supported by chronic toxicity data in other species.

Using 0.21 mg/day as the ADI, and assuming the 70-kg adult consumes two liters of drinking water per day, the AADI is calculated as follows:

AADI:

$$\frac{0.21 \text{ mg/day}}{2 \text{ L/day}} = 0.1 \text{ mg/L}$$

Since this AADI is based upon observations in humans, it is assumed that additional molybdenum exposure results from other sources (i.e., food and air). Thus, the calculated ADI and AADI represent an estimate of the molybdenum exposure limit associated with drinking water and no further consideration of relative source contributions is necessary.

C. Carcinogenic Effects

The only molybdenum compound that has been observed to produce tumors in animals is the inorganic pigment, Molybdenum Orange, which is a mixture of lead chromate, sulfate and molybdate (Maltoni et al. 1982). In this work, doses of 30 mg of the compound in 1 mL of saline were administered to 20 male and 20 female Sprague-Dawley rats, 13 weeks old. The dose was delivered by subcutaneous injection. After 117 weeks, 90% of the animals had developed a sarcoma at the injection site. None of the controls that received 1 mL of saline developed a sarcoma at the injection site. However, since both lead and chromate are contained in this pigment, it is not possible to conclude that the effect was due to molybdenum. Further, the relevance of this effect is questionable with regard to oral exposure via drinking water.

D. Quantification of Carcinogenic Effects

Due to lack of sufficient evidence on the carcinogenic potential of molybdenum in animals or humans, no quantification of carcinogenic effects for molybdenum can be made.

E. Existing Guidelines and Standards

The World Health Organization has not established or recommended a limit for molybdenum in drinking water. The U.S.S.R has apparently established a limit of 0.5 mg Mo/L in "open" water (NAS 1977). The Threshold Limit Value (TLV) set by the American Conference of Governmental Industrial Hygienists (ACGIH 1980) for soluble molybdenum compounds is 5 mg Mo/m^3. The TLV represents a maximum average concentration in the workplace air which represents no hazard to the health of the workers during their lifetime. The National Academy of Sciences report on recommended dietary allowances (NAS

1980) sets forth recommended adequate and safe intakes for molybdenum. For infants, age 0 to 0.5 year these are 0.03 to 0.06 mg/day and increase to 0.15 to 0.5 mg/day for the population consisting of adults and children 11 years old and over.

F. Special Considerations

1. High Risk Populations

Molybdenum ingestion is associated with depleted copper stores in the body. Thus, humans who have an inadequate intake of dietary copper, or some dysfunction in their copper metabolism that tends to make them copper-deficient, could be at greater risk of molybdenum toxicity than the general population. The importance of the kidney in regulating molybdenum excretion suggests that humans with renal dysfunction might also be at increased risk. Evidence to support this view is provided by Smythe et al. (1982). The research by Tsongas et al. (1980) demonstrated that the daily dietary intake of Mo/kg was two to three times higher for one- to eight-year-old children than for adults. Whether this establishes children as a high-risk population, however, is not known.

2. Interactions

The interaction of copper, molybdenum and sulfur is quite complex and is still not completely understood. In monogastric animals, added sulfate in the diet tends to decrease the toxic effects of molybdenum, but added sulfide in the diet can exacerbate the effect of molybdenum, particularly in an animal that is deficient in copper (Mills et al. 1981).

The antagonistic effects of molybdenum with respect to copper are discussed earlier (see High Risk Populations).

3. Beneficial Effects

While there is evidence that molybdenum is a necessary micronutrient, the daily requirement is apparently very low (there has been only one report of a deficiency that occurred during total parenteral nutrition). Because of the presumed essentially of molybdenum, NAS (1980) has established an adequate and safe intake level for molybdenum of 0.15 to 0.5 mg Mo/day for adults and older children (11 years old and above).

G. Summary

The recommended values for the one-day and ten-day HAs for both adults and children, and the AADI are summarized in Table VIII-4.

Table VIII-4 Summary of Quantification of Toxicological Effects

	Drinking water concentration (mg/L)		
	10-kg child	70-kg adult	Reference[a]
One-day Health Advisory	2.7	9.5	Fairhall et al. 1945
Ten-Day Health Advisory	0.3	1.0	Fairhall et al. 1945
AADI	--[b]	0.1	Chappell et al. 1979

[a] Reference for NOAEL used in calculating HA or AADI values.

[b] Not calculated because the child will not remain in the high risk population for a lifetime.

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